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Valvular Pulmonic Stenosis with Intact Ventricular Septum and Patent Foramen Ovale

Report of Illustrative Cases and Analysis of Clinical Syndrome

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In this malformation the difficulty in sending blood through the stenosed pulmonary valve leads to right heart enlargement and to functional patency of the foramen ovale, through which a venous-arterial shunt occurs. The onset of symptoms and their severity depend on the size of the opening in the pulmonary valve. Characteristic physical findings and results of fluoroscopy, electrocardiogram, circulation time, arterial blood studies, exercise test, angiocardiogram, and cardiac catheterization are presented. Diagnosis is important because these patients develop cardiac failure following a Blalock-Taussig operation, but may be greatly helped by pulmonic valvulotomy.

VALVULAR pulmonic stenosis with an intact ventricular septum occurs less frequently than pulmonic stenosis associated with a ventricular septal defect and an overriding aorta, as in the tetralogy of Fallot. Greene and co-workers[1] after a thorough search of the literature found 68 cases proved by autopsy in which the auricular as well as the ventricular septum was intact. In the remainder of the cases of "pure pulmonic stenosis" the foramen ovale was not completely sealed. This, however, is not necessarily a malformation as the foramen ovale remains patent in a number of "normal" persons.

The first case of valvular pulmonic stenosis and patency of the foramen ovale was reported by Gallois[2] in 1809 and is included in Paul's review[3] describing three similar cases. Maude Abbott[4] in her collection of 1000 cases of congenital malformations of the heart listed 16 additional patients with this malformation. Currens, Kinney, and White,[5] from a survey of the autopsy specimens obtained from several Boston hospitals, reported 10 cases with pure pulmonic stenosis, of which 5 had an associated patency of the foramen ovale and an additional case had fenestrations in the septum secundum. Selzer and associates[6] have recently reviewed the literature and studied 2 adults who died with this malformation. In addition to those included in Selzer's review, autopsied cases have been reported by Wilson,[7] Auerback and Stemmerman,[8] Mannheimer,[9] Brock,[10] Baker and associates,[11] and Allanby and Campbell.[12]

Although the condition has been recognized at the autopsy table for the past 140 years, the correct diagnosis has rarely been made during life. In the past several years we have had the opportunity to study a group of these patients. Although the clinical picture was at first puzzling, it was recognized that the findings in all were quite similar and that all had the same malformation. Subsequent cor-

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relation of these findings with postmortem examinations clarified the clinical syndrome. Correct clinical diagnosis is of considerable importance because patients with this type of pulmonic stenosis are not benefited by the Blalock-Taussig operation but are helped by pulmonic valvulotomy. The purpose of this paper is to present the clinical syndrome associated with this malformation. The following cases are selected as representative examples.

FIG. 1. Case 1. Anterior-posterior view of chest. Note cardiac enlargement, prominence of pulmonic conus, large left pulmonary artery, and diminished vascularity of peripheral lung fields.

Case 1. W. W. (H. L. H. A 56312), a 24 year old white man, was first examined in July, 1947.

Past History and Present Illness. He had had exertional dyspnea for as long as he could remember, and had always tired more readily than other people. The first knowledge of heart trouble dated from 8 years of age, when after a race, he became cyanotic and extremely dyspneic. At that time he was told that he had "leakage of the heart." Thereafter severe exertion produced cyanosis as well as marked dyspnea. He did not, however, squat when tired. His activities were only slightly restricted. He served during World War II in the Merchant Marine.

The development of persistent cyanosis was insidious; the patient was not aware of it until January, 1947, when he was admitted to a hospital because of a left-sided hemiplegia which developed suddenly 16 days after being rendered unconscious in an automobile accident. At that time he was found to be moderately cyanotic and to have clubbing of the fingers. Subsequently the hemiplegia cleared almost completely. However, following this episode, his incapacity, cyanosis, and dyspnea became progressively more severe and he occasionally suffered from swelling of the ankles. In June, 1947, he was found to have a right pneumothorax. After the lung had re-expanded, he was referred to the Cardiac Clinic as a possible candidate for cardiac surgery.

Physical Examination. Pulse 102 per minute; respirations 20 per minute; blood pressure 124/94. The patient was a well-developed, well-nourished man with moderate cyanosis and clubbing of the fingers and toes. There was anterior bowing of the left chest. No thrill was palpable over the precordium. The heart was enlarged. The heart sounds were distinct though less loud than normal. The second sound was louder over the pulmonic area than over the aortic area but was not accentuated. There was a harsh but rather soft, blowing systolic murmur best heard in the third and fourth intercostal spaces to the left of the sternum. It was transmitted over the entire precordium and to the left interscapular area posteriorly. There was a presystolic gallop rhythm. The lungs were clear. The liver extended 2 fingerbreadths below the costal margin and was pulsating. The pulsations in the femoral arteries were strong. There was no edema. Except for a residual left facial paralysis the remainder of the physical examination was negative.

Laboratory Data. The red blood cell count was 7.68 million per cu. mm.; the hemoglobin level was 19.8 Gm. per 100 cc. and the hematocrit reading was 65. The oxygen content of the arterial blood was 23.4 volumes per cent and the oxygen capacity was 30.1 volumes per cent; hence the saturation was 78.3 per cent. The arm-to-tongue circulation time, determined with Decholin, was prolonged to 18.7 seconds. Electrocardiogram showed high peaked P waves, incomplete A-V block, and right bundle branch block.

Fluoroscopy in the anteroposterior view showed that the heart was enlarged to the right and to the left. In the oblique views the cardiac shadow extended abnormally far both anteriorly and posteriorly. These findings were thought to indicate enlargement of the right auricle, the right ventricle, and the left ventricle. The right ventricular pulsations were of exceedingly small amplitude. The pulmonary conus was prominent, and the pulmonary window was obscured. The lung vascular markings, however, appeared reduced, and only very slight pulsations could be seen in the hilar vessels. There was a left aortic arch and no left auricular enlargement. Teleroentgenogram showed the cardiothoracic ratio was 57 per cent (fig. 1).

Since the nature of the malformation was not clear, additional studies were undertaken. An *exercise test* showed a drop in the amount of oxygen consumed per liter of ventilation from 24.7 cc. at rest to 18.6 cc. after exercise. There was a corresponding decrease in carbon dioxide production from 23.1 to 20.9 cc.

Catheterization of the right heart was attempted on

two occasions, but on neither occasion could the catheter be introduced into the right ventricle. The right auricular pressure was elevated to 29/15 mm. Hg.

Angiocardiogram showed that the Diodrast entered via a dilated superior vena cava into a large right auricle and a large thick-walled right ventricle. The dye was expelled very slowly from the right side of the heart into a dilated pulmonary artery, where it lingered for an abnormally long time before being distributed to the lungs. Because the right pulmonary artery was hidden behind the enlarged heart, it was at first thought that there was but a single pulmonary artery. No evidence of overriding of the aorta was demonstrable and the left side of the heart was never visualized. The dye still remained in the right heart and pulmonary artery at the end of the series of angiocardiograms. (The last of these x-rays was taken about 11 seconds after the injection of the dye.)

Clinical Impression. It was thought that the patient had pulmonic stenosis and tricuspid insufficiency; the possibility of Ebstein's malformation of the tricuspid valve was considered. A Blalock-Taussig operation was contraindicated because of the enlarged heart, the poor heart action, the pulsating liver, and the failure to demonstrate an overriding aorta.

Course. The patient was given digitalis and a period of bed rest was advised. In spite of therapy he became more dyspneic, cyanotic, and incapacitated. In October, 1947, he was able to walk only four blocks very slowly before becoming exhausted. At this time his arterial oxygen saturation at rest had dropped to 53 per cent. He developed multiple emboli to the right leg, to the brain, and to the lungs. On March 16, 1948 he was admitted to the U. S. Marine Hospital in Seattle, Washington in moribund condition and he died 15 hours later.

Autopsy. (Performed by Dr. George E. Tooley,* U. S. Marine Hospital, Seattle, Washington). The heart was markedly enlarged; it weighed 725 Gm. (normal 300 Gm.) (See figure 2.) The great veins entered in the normal fashion. The right auricle was tremendously dilated, and its walls were moderately hypertrophied. There was a gross patency of the foramen ovale which measured 6 by 8 mm. The tricuspid valve measured 12.5 cm. and was normal in appearance. The right ventricle was enormously hypertrophied. The myocardium had an average thickness of 2.4 cm. in contrast to an average thickness of the left ventricle of 1.2 cm. Microscopically the right ventricle showed diffuse myocardial scarring. There was marked stenosis of the pulmonary valve (fig. 3). The cusps of the pulmonary valve were completely fused into a dome-shaped membrane with only a small central opening measuring 2 by 4 mm. Below the stenotic pulmonary valve

FIG. 2. Case 1. Photograph of heart, showing enlarged right auricle and right ventricle. Patent foramen ovale is indicated by pointer. Hypertrophy of right ventricular musculature is apparent.

FIG. 3. Case 1. Photograph of heart. Note dome-shaped protrusion of stenosed pulmonary valve and small, central perforation in the fused cusps. The dilated pulmonary artery has been laid open.

was a mural thrombus firmly adherent to the endocardium over an area 2 by 3 cm. The pulmonary arteries appeared dilated. The left auricle, mitral valve, and left ventricle were normal. There was no ventricular septal defect. The aorta arose from

* We are indebted to Dr. Gordon A. Abbott, Clinical Director of the Marine Hospital, for the photographs of the specimen and the pathology report and to Dr. Stewart Lippincott, Professor of Pathology at the University of Washington Medical School, for permitting us to study the specimen.

the left ventricle in the normal manner, and both the aortic valves and the aorta were normal. There was generalized visceral congestion. The liver was enlarged. Both the liver and spleen showed gross and microscopic evidence of long-standing passive congestion.

Final Anatomic Diagnosis. Congenital malformation of heart. Valvular pulmonic stenosis. Poststenotic dilatation of pulmonary artery. Patent foramen ovale. Hypertrophy of right ventricle. Dilatation and hypertrophy of right auricle. Mural thrombus in right ventricle. Passive congestion of viscera. Congestive cirrhosis of liver.

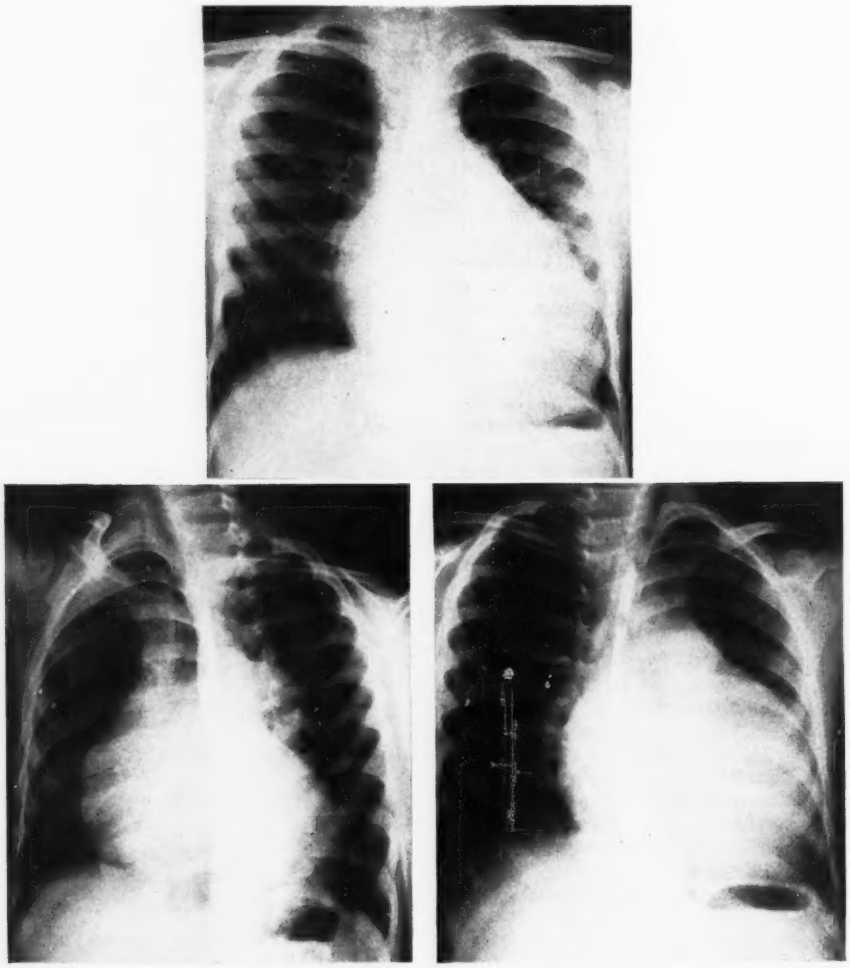

FIG. 4. Case 2. *Top:* Anterior-posterior view of chest. Note great cardiac enlargement and prominence of pulmomary conus. *Bottom left:* Left anterior-oblique position at 55 degrees of rotation. Note extent to which enlarged right ventricle has displaced the left ventricle posteriorly. Dilated pulmonary artery fills the pulmonary window. *Bottom right:* Right anterior-oblique position. The greatly enlarged right ventricle is flattened against left anterior chest wall. The barium-filled esophagus crosses the enlarged right auricle, which projects posteriorly.

Case 2. D. L. (H. L. H. A 62640), a 6 year old white boy, was first seen in the Cardiac Clinic in May, 1948.

Past History and Present Illness. There was no cyanosis at birth or in early infancy, but at about 6 months of age cyanosis and dyspnea appeared on exertion. At this time a systolic murmur was noted.

At 18 months of age cyanosis became persistent, and thereafter it steadily increased. He easily became dyspneic and fatigued, but he squatted to rest only infrequently. His exercise capacity gradually became more limited. At 6 years of age he was able to walk only three blocks on a good day and was tired after climbing one flight of stairs. There were no episodes of paroxysmal dyspnea, loss of consciousness, or convulsions. The family physician noted progressive cardiac enlargement.

Physical Examination. Temperature 37 C.; pulse 96 per minute; respiratory rate normal at rest; blood pressure 100/80. He was slender but well developed. There was moderate cyanosis and clubbing of the fingers and toes. There was a precordial bulge. The heart was enlarged but no thrill was palpable. There was a soft, blowing, systolic murmur in the third intercostal space at the left sternal border. The second sound at the base of the heart was weak. The liver edge was 2 fingerbreadths below the right costal margin and was pulsating. The pulsations in the femoral arteries were strong. There was no edema. The remainder of the examination was essentially negative.

Laboratory Findings. The red blood cell count was 6.75 million per cu. mm.; the hemoglobin level was 22 Gm. per 100 cc.; the hematocrit reading was 56. The arterial oxygen content was 19.2 volumes per cent; the capacity was 24.4 volumes per cent, giving an arterial oxygen saturation of 78.8 per cent. The arm-to-tongue circulation time with Decholin was 12 seconds. In the unipolar and standard leads, the electrocardiogram showed high, peaked P waves, first degree heart block, and right bundle branch block.

Fluoroscopy in the anteroposterior view revealed that the heart was moderately enlarged to the right and to the left (fig. 4). There were strong, asynchronous pulsations of the right and left cardiac borders. There was a convexity in the region of the pulmonary conus, and a large left pulmonary artery was seen to continue from this point into the left lung. The right pulmonary artery appeared to be of normal size. There were no expansile pulsations visible in either pulmonary artery, and the lung fields were abnormally clear. In the oblique views (fig. 4) there was evidence of great enlargement of the heart both anteriorly and posteriorly. Barium swallow showed a left aortic arch and no enlargement of the left auricle. Teleroentgenogram revealed the cardiothoracic ratio to be 69 per cent.

Clinical Impression. Valvular pulmonic stenosis with a patent foramen ovale was considered the most probable diagnosis. Ebstein's anomaly of the tricuspid valve was considered a possibility. To differentiate the two conditions and to clarify the diagnosis, additional studies were undertaken.

Angiocardiogram (fig. 5) showed that the Diodrast entered the right auricle through the dilated superior vena cava and passed into the large, thick-walled right ventricle. At the end of two seconds, the contrast medium appeared in the main pulmonary artery, which occupied the position of the prominent pulmonary conus seen on fluoroscopy. The contrast solution remained in the right side of the heart and in the pulmonary artery for an abnormally long time. The opacification of the parenchymal pulmonary vascular tree was less than normal. No overriding of the aorta was demonstrated. The left side of the heart was poorly visualized.

*Right heart catheterization** revealed that the oxygen content of the superior vena cava was 9.2 volumes per cent and of the right auricle, 8.4 volumes per cent in one region and 12.2 volumes per cent in another location. The oxygen content of the right ventricle was 12.2 volumes per cent. The pulmonary artery could not be catheterized. The pressure in the right auricle was elevated, and in the right ventricle it was 112/55. Calculation of the blood flows showed a reduced pulmonary artery flow of 1280 cc. and a systemic flow of 1830 cc. per square meter of body surface per minute. Although there was a small shunt of oxygenated blood from the left auricle into the right auricle, as indicated by the higher oxygen content of one of the samples taken from the right auricle, the overall shunt was from right to left and was calculated to be 550 cc. per square meter of body surface per minute. Thus catheterization studies were consistent with the clinical impression of valvular pulmonic stenosis and patency of the foramen ovale.

Course. The catheterization procedure was a short one, and the patient returned to the ward in good condition. Shortly afterwards, he appeared restless. He was examined by several doctors and given a small dose of morphine. His condition was thought to be satisfactory. Suddenly, about three hours after completion of the catheterization, he gasped, became deeply cyanotic, and the respirations and heart action ceased. Resuscitative measures were of no avail.

Autopsy. (No. 21233 performed by Dr. Jack M. Burnett.) The chief interest centered about the enlarged heart. The enlargement was limited to the right auricle and the right ventricle, which formed the anterior surface of the heart. Venous return was normal. The right auricle was hypertrophied and was about twice the size of the left auricle. Although in part protected by a thickened valve, the foramen ovale was patent for an area of 2 by 8 mm. The tricuspid valve was bicuspid but competent; its edges were slightly thickened. The right ventricle was greatly hypertrophied. Its wall in some areas measured 2.5 cm. in thickness, whereas the thickness of the left ventricle was 1.2 cm. Near the apex of the right ventricle there was patchy scarring of the myocardium. The endocardium was

* We are indebted to Dr. Richard Bing and his associates for these studies.

uniformly slightly thickened. The ventricular septum was intact. The leaflets of the pulmonic valve were completely fused, producing a conical protrusion into the pulmonary artery. There was a small opening 2 mm. in diameter at the apex of the cone. The main pulmonary artery distal to the stenosed valve was about twice the usual diameter, and its walls were thin. The left auricle and left ventricle, the mitral and aortic valves, the aorta, and the coronary arteries were normal. The ductus arteriosus was obliterated. The bronchial arteries were slightly enlarged; their lumina each measured 1 mm. in diameter. The remainder of the postmortem examination was not remarkable.

Anatomic Diagnosis. Congenital malformation of heart. Valvular pulmonic stenosis. Poststenotic dilatation of pulmonary artery. Patent foramen ovale. Hypertrophy of right ventricle and of right auricle.

Case 3. C. N. S., (H. L. H. A 65191), a 2 year old white girl, referred to the Cardiac Clinic in August, 1948.

Past History and Present Illness. Cyanosis was noted at birth, and it progressively deepened. Dyspnea appeared after moderate exertion, but there were no attacks of paroxysmal dyspnea, and she did not assume a knee-chest position when fatigued. She was unable to walk. From the age of 8 months she gained weight poorly. At the time of her examination in the clinic, the mother felt that the child's condition was gradually deteriorating.

Physical Examination. Temperature 37 C.; pulse 140 per minute; respirations 30 per minute; blood

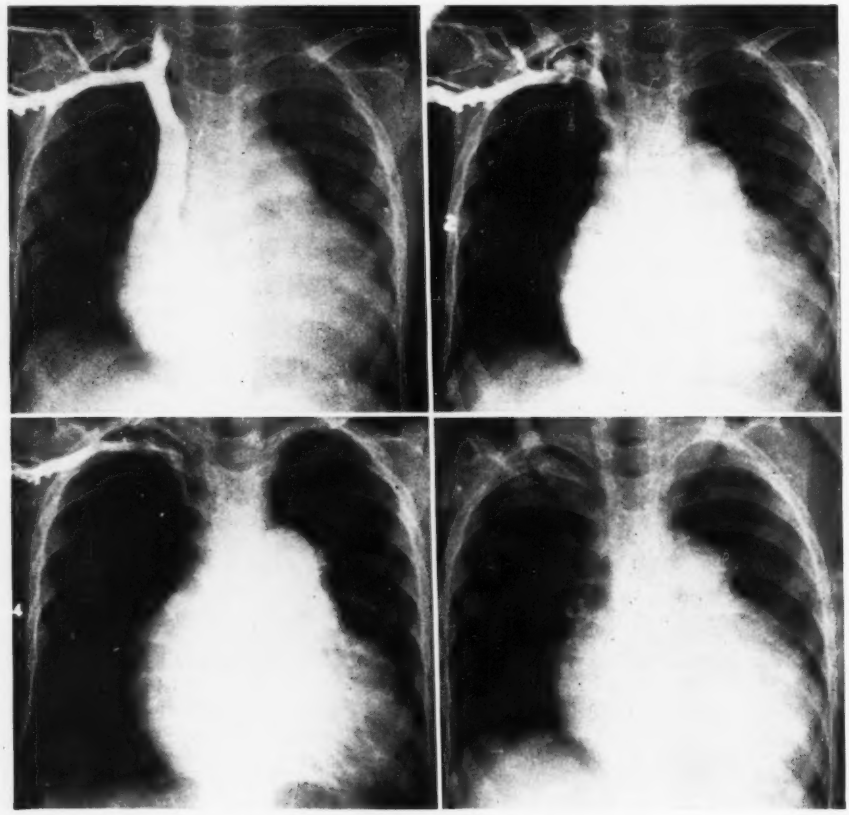

FIG. 5. Case 2. Angiocardiogram, anterior-posterior view. *Top left:* 1 second. Contrast medium is seen in the dilated superior vena cava and in the right auricle. *Top right:* 2 seconds. Dye has entered the right ventricle and pulmonary artery. *Bottom left:* 4 seconds. Dense opacification of right auricle, right ventricle, and pulmonary artery with beginning visualization of larger branches of pulmonary artery. *Bottom right:* 7 seconds. Diodrast remains in right heart chambers and main pulmonary artery. There is still subnormal filling of pulmonary circulation.

pressure 114/70 in the arm and 118/78 in the leg. She was a small, underdeveloped child who weighed only 24½ pounds at the age of 2 years. There was slight clubbing of the fingers and toes, and even at rest there was cyanosis. With crying she became dyspneic and markedly cyanotic. Examination of the chest showed no precordial bulge; no thrill was felt. The heart was enlarged; the heart sounds were of good quality. In the third intercostal space to the left of the sternum was a loud, harsh, systolic murmur which was propagated over the precordium and upward to the left shoulder; over the pulmonic area it obscured the second heart sound. The liver was palpable one fingerbreadth below the costal margin and was pulsating. There was no edema. The remainder of the physical examination was negative.

Laboratory Findings. The red blood cell count was 9.55 million per cu. mm., the hemoglobin level was 21.5 Gm. per 100 cc. and the hematocrit reading 76. A sample of femoral arterial blood, obtained when the child was crying, revealed an arterial oxygen saturation of only 14 per cent. The oxygen content was 3.1 volumes per cent, the oxygen capacity 21.2 volumes per cent, and the carbon dioxide content 36.8 volumes per cent. The electrocardiogram showed marked right axis deviation. There were high, peaked P waves, first degree heart block, and evidence in the unipolar precordial leads of right bundle branch conduction disturbance. T_2 and T_3 and the T waves in the precordial leads were deeply inverted.

Fluoroscopy revealed a heart that was tremendously enlarged both to the right and left in the anteroposterior view, and both anteriorly and posteriorly in the left anterior-oblique position. The pulmonary conus region was full; there were, however, no pulsations in the pulmonary arteries, and there was diminished vascularity of the lung fields. There was a left aortic arch. No enlargement of the left auricle was demonstrated after barium swallow. The fluoroscopic findings were interpreted as indicative of diminished pulmonary circulation and great enlargement of the right auricle and right ventricle and questionable enlargement of the left ventricle. Teleroentgenogram showed the cardiothoracic ratio was 81 per cent (fig. 6).

Clinical Impression. Valvular pulmonic stenosis with a patent foramen ovale or an auricular septal defect.

Course. Angiocardiography was undertaken to confirm the diagnosis. The patient showed no reaction to the test dose of Diodrast; so after a cutdown in the right arm, 9 cc. of the Diodrast was injected and a series of anteroposterior films taken. The contrast medium entered through a dilated superior vena cava into a very large right auricle and then into the large, thick-walled right ventricle. Some of the Diodrast filled the main pulmonary artery, which occupied the region of the full pulmonary conus, and a small amount of contrast medium entered the larger branches of the pulmonary circulation. The right side of the heart emptied very slowly. The dye was still present in the right ventricle and main pulmonary artery at the conclusion of the series of films seven seconds after start of injection. Neither the aorta nor the left side of the heart was visualized by this time.

The patient seemed well immediately following the procedure, but five minutes later she suddenly stopped breathing, and the heart sounds could not be heard. Resuscitative efforts were futile.

FIG. 6. Case 3. Anterior-posterior view of chest. Note tremendous cardiac enlargement and the fullness in region of pulmonic conus.

Autopsy. (No. 21480 performed by Dr. Lloyd Shannon). The heart was greatly enlarged, its tremendous size being due entirely to the large right auricle and right ventricle, which formed the anterior aspect of the heart. The heart weighed 140 Gm. (normal 50 Gm.). Venous return was normal. The right auricle was extremely dilated and its wall moderately hypertrophied. The foramen ovale was widely patent, measuring 2 cm. in diameter. The tricuspid valve was bicuspid. The right ventricle was markedly hypertrophied. Its wall measured 1.8 cm. in thickness, whereas the wall of the left ventricle measured 1 cm. The ventricular septum was intact. The pulmonary valve was extremely stenosed. The valve cusps were fused to such a degree that they formed a cone with only a pinpoint opening about 1 mm. in diameter at the apex of the cone. The pulmonary artery distal to the valve was dilated and was of approximately the same size as the aorta. The left side of the heart and the aorta were normal. There was probe patency of the small ductus arteriosus. Two of the bronchial arteries were slightly enlarged. The spleen was enlarged, but the liver was normal.

No cause for the sudden death was found. The lungs were well aerated. There were no evidences of air emboli. The trachea and bronchi were free from obstruction. Examination of the cranial cavity revealed no abnormalities.

Anatomic Diagnosis. Congenital malformation of heart. Valvular pulmonic stenosis. Poststenotic dilatation of pulmonary artery. Patent foramen ovale. Hypertrophy of right auricle and right ventricle. Probe patency of ductus arteriosus.

Discussion

These three cases illustrate the clinical syndrome, which is readily explicable on the basis of the pathologic anatomy. The stenosed pulmonary valve places a tremendous load on the right side of the heart and causes difficulty in the expulsion of blood into the pulmonary artery. This leads to hypertrophy of the right ventricle and to progressive increase in the systolic pressure. Gradually the right ventricle becomes unable to empty itself completely, and the diastolic pressure within the ventricle rises. This in turn increases the work of the right auricle; consequently, the right auricle hypertrophies, and the pressure within that chamber rises.

When the pressure in the right auricle exceeds that in the left auricle, if the foramen ovale is not completely sealed, it is forced open, and venous blood is shunted from the right auricle into the left auricle. When the volume of unoxygenated blood so shunted into the systemic circulation is sufficiently large, the level of visible cyanosis is reached. The cyanosis is at first transitory, then becomes persistent, and deepens as the patient grows older. As the volume of the venous-arterial shunt increases, polycythemia appears. The increase in the height of the hemoglobin level renders the cyanosis more intense.

At birth there probably is less tendency for the foramen ovale to close than in a normal heart. However, so long as the pulmonary orifice is relatively adequate in size and the pressure in the right auricle is lower than in the left auricle, the valve of the foramen ovale is functionally closed.

The patency of the foramen ovale is the only means by which an intracardiac venous-arterial shunt can occur in this malformation. The evidence is strong that without such a shunt, there is no decrease in arterial oxygen saturation. It has been well demonstrated that a diminution in pulmonary circulation *per se* will not produce arterial unsaturation. In those patients with pulmonic stenosis as part of the tetralogy of Fallot in whom Bing was able to catheterize the pulmonary vein, he found the oxygen saturation of the pulmonary vein to be normal (95 to 96 per cent).[13] Indeed, in one of our patients with valvular pulmonic stenosis and a patent foramen ovale to be included in a subsequent report,[14] the pulmonary vein was catheterized, and its oxygen saturation was found to be 97 per cent.

Analysis of the findings in our patients and those in the literature corroborates the belief that in this condition the cyanosis due to arterial oxygen unsaturation is related to the patency of the foramen ovale. The foramen ovale was patent in 41 cases previously reported.[3-12, 15-18] Of these patients on whom clinical data is available, 35 showed cyanosis, and only 1 did not.[5] The last mentioned was a 4½ month old baby who died of an unrelated cause (subdural hematoma). In this instance, although there was probe patency of the foramen ovale, it appeared to be functionally closed.

Of the 71 patients[1, 12] with pulmonic stenosis and no defect in the auricular and ventricular septa, cyanosis of slight degree was commented upon in 29. As there was no opportunity for a venous-arterial shunt in these patients, the cyanosis was in all probability not due to arterial oxygen unsaturation. On the contrary, it seems quite likely that cyanosis was caused by venous stasis. That such may be the cause is well illustrated by Arnett's patient,[19] who when decompensated showed splotchy cyanosis of the ear lobes, the tip of the nose, and the cheeks. His arterial oxygen saturation, however, was 94.6 per cent. At autopsy the foramen ovale, though not sealed, was closed and was guarded on both sides by large folds.

The elevated pressure in the right side of the heart in patients with pulmonic stenosis with an intact ventricular septum eventually causes venous congestion and enlargement of the liver, and ultimately, if the right ventricle fails, may

lead to peripheral edema and ascites. The patency of the foramen ovale acts for a time as an "escape valve" and lessens the load on the right side of the heart by the shunt of blood from the right auricle into the left. Even while the tricuspid valve remains competent, the forceful contractions of the right auricle may cause pulsations of the jugular veins and the liver.

It seems probable that the size of the opening in the fused pulmonary leaflets is fixed at birth and does not increase in size as rapidly as does a normal valve. What may be a relatively adequate pulmonic opening for a small, inactive infant becomes progressively less adequate as the patient grows and his activity increases. As the stenosis thus becomes increasingly more severe, the heart progressively enlarges, and symptoms appear and steadily become more pronounced. The smaller the orifice of the stenotic valve, the earlier is the onset of cardiac difficulties. If the stenosis is extreme at birth, the pulmonary orifice may be inadequate even for a baby, and the patient may die in infancy or early childhood. This concept explains the variations in longevity and in severity of symptomatology in these patients. The average age at death of those reported in the literature was 19 years, but the range was from 4 months[15] to 57 years.[3]

The primary symptom is dyspnea on exertion; this is usually present from early life. It generally precedes the onset of cyanosis and is out of proportion to the cyanosis. It is due to the difficulty in the direction of blood to the lungs. As the shunt of blood through the foramen ovale from the right auricle to the left becomes established and the pulmonary flow is thereby diminished, exertional dyspnea becomes more pronounced. The easy fatigability is also related to the slow delivery of blood to the lungs for oxygenation. The pulmonary stenosis renders it impossible for the individual to increase the pulmonary blood flow in the normal manner with exercise.

The physical findings are readily explicable on the basis of the pulmonary stenosis. The presence of a precordial bulge is due to the hypertrophy of the right ventricle during early childhood. The systolic murmur, maximal in the pulmonic area, is caused by the ejection of blood through the stenosed pulmonary orifice. The stenosis of the pulmonary valve causes a reduction in the intensity of the second sound over the pulmonary area. Enlargement and pulsations of the liver are manifestations of the hypertrophy of the right side of the heart and the high pressure in the right auricle.

The electrocardiographic findings of marked right axis deviation and right ventricular hypertrophy and the frequent finding of right bundle branch block are related to the increased thickness of the right ventricular wall and possibly to the diffuse scarring of the right ventricular myocardium. The high, peaked P waves probably reflect the enlargement of the right auricle. Arterial oxygen unsaturation is present after the shunt from right to left through the foramen ovale has become established. This in turn leads to compensatory polycythemia. The prolonged circulation time is related to the difficulty in the expulsion of blood from the right ventricle. It has been our clinical experience that although the foramen ovale is patent, rarely is enough of the test material shunted from the right auricle through the left auricle and thence to the left ventricle and the systemic circulation to give a short circulation time.

The x-ray and fluoroscopic findings are also explicable on the basis of the pulmonic stenosis. There is progressive enlargement of the right ventricle and the right auricle. On rotation of the patient into the left anterior-oblique position the left ventricle is often displaced so far posteriorly by the large right ventricle that it far overlaps the spine and gives the appearance of enlargement of both the right and left ventricles (see figure 4). The force of contraction in the right auricle and right ventricle seen on fluoroscopy is worthy of comment. Often a "rocking boat" effect is seen in the anteroposterior view as first the right auricle, forming the right heart border, contracts forcefully, and then the hypertrophied right ventricle, forming the left heart border, contracts. The amplitude of the pulsations has been conspicuous in all but 2 of our patients (case 1 and another not included in this report). Moreover, in these 2 the pulsations of the right

auricle were strong, whereas the contractions of the right ventricle were so weak that pulsations were scarcely visible. This finding was a late manifestation, as indicated by the fact that both patients died within a few months after such pulsations were seen. This observation suggests that when the hypertrophied right ventricular musculature begins to fail, the force of its contractions becomes much reduced. Consequently, such a finding is of grave prognostic importance.

Although there is a prominence of the pulmonic conus region and the pulmonary arteries are normal in size or enlarged, pulsations in the pulmonary arteries are absent or minimal, and the peripheral lung vascular markings are diminished. These findings are in keeping with the low pressure in the pulmonary artery. The prominence of the conus region was demonstrated both by angiocardiogram during life and by postmortem examination to be due to the dilatation of the pulmonary artery distal to the valvular stenosis. This poststenotic dilatation may be the result of the ejection of a small volume of blood with each ventricular contraction into a pulmonary artery that was originally normal in size. The force of the ejection is almost completely broken by the pulmonary stenosis so that only a thin jet of blood enters the pulmonary artery through the small central perforation. As there is little force to distribute the blood into the pulmonary circulation, the blood pools in the main pulmonary artery before it sluggishly circulates through the lungs.

The finding on angiocardiography* of delay of the dye in the right side of the heart and in the pulmonary arteries reflects the difficulty in expulsion of blood from the right ventricle forward into the pulmonary circulation. Early visualization of the aorta does not occur until some of the contrast solution has passed from the right auricle through the defect in the auricular septum to the left. The volume so shunted is relatively small, and the aorta is often visualized in only one of the two series of films taken in the anteroposterior and in the lateral positions. Although there may be faint opacification of the aorta, there is not the dense, early filling which is seen when the aorta overrides the right ventricle.

Because of the pulmonic stenosis and the inability to increase the pulmonary blood flow with exercise, the exercise test usually shows a drop in the oxygen consumption per liter of ventilation with exercise compared with that at rest. The measurement on cardiac catheterization of an elevated pressure in the right auricle and particularly in the right ventricle and of a low pressure in the pulmonary artery is in keeping with the hemodynamic changes proximal and distal to an obstruction at the pulmonary valve.

This malformation requires differentiation from other malformations of the heart which are associated with cyanosis and inadequate pulmonary circulation. The two chief malformations with which it is likely to be confused are the tetralogy of Fallot and Ebstein's malformation of the tricuspid valve.

The differentiation from the tetralogy of Fallot is important because, while the latter malformation is dramatically helped by the Blalock-Taussig operation, each of the 3 patients with valvular pulmonic stenosis who were operated upon because of an erroneous diagnosis of tetralogy of Fallot failed to do well after operation. Although the dyspnea and cyanosis were improved after the circulation to the lungs was increased, the increased volume of blood returned to the left auricle tended to close the valve of the foramen ovale, and thereby increased the strain on the right side of the heart. In each of the above-mentioned patients operation caused tremendous cardiac enlargement and cardiac failure with a huge pulsating liver.

These patients have since been reoperated upon, 2 by Mr. Brock and 1 by Dr. Blalock. The pulmonic stenosis was approached directly through the right ventricle, and the pulmonic

* Because of the death of one patient (case 3) immediately following angiocardiography, we feel this procedure is dangerous in patients with extreme pulmonary stenosis and impending heart failure, as indicated by a very low arterial oxygen saturation, great cardiac enlargement, or poor amplitude of pulsations in the right ventricle. Under such circumstances the sudden injection of contrast material under pressure may add too great a load to the already overtaxed right heart and may deprive the patient of oxygen.

valve was cut; subsequently, the subclavian-pulmonary artery anastomosis was closed. The first patient was in severe heart failure and had recently developed a hemiplegia. He died immediately after the operation. The diagnosis of valvular pulmonic stenosis with patency of the foramen ovale was confirmed at autopsy. The other 2 patients were greatly improved. In each instance the liver promptly receded and ceased to pulsate, and the patient regained compensation. The arterial oxygen saturation rose to nearly normal levels, the symptoms were alleviated, and the patients have done well. Pulmonic valvulotomy has since been performed with gratifying results on other patients with this malformation. These will be reported at a later date.[14]

The clinical picture presented by the tetralogy of Fallot is quite distinct from that produced by valvular pulmonic stenosis with a patent foramen ovale. The absence of marked cardiac enlargement and the concave curve in the pulmonary area, the absence of pulsations of the liver, and the short circulation time differentiate the tetralogy of Fallot from "pure" pulmonic stenosis. The following features are also helpful. In the tetralogy cyanosis and dyspnea are proportionate to each other and usually appear in early infancy. Attacks of paroxysmal dyspnea are common. The patient typically assumes a squatting position to rest. The electrocardiogram shows right axis deviation and right ventricular hypertrophy; however, there is usually no prolongation of auriculoventricular or of intraventricular conduction time. In doubtful cases either angiocardiography or cardiac catheterization aid in the differentiation of the two malformations.

This clinical syndrome even more closely resembles that due to Ebstein's anomaly of the tricuspid valve with patency of the foramen ovale.[20] This malformation is not amenable to surgery. It is differentiated by the following features. In Ebstein's anomaly cyanosis is more marked than the dyspnea. The heart sounds usually are of poor quality, often there is a gallop rhythm, and there may be a diastolic murmur in addition to the systolic murmur. The liver may be enlarged, but unless the patient is in heart failure, there are no pulsations palpable at its margin. On fluoroscopy there is an absence of fullness in the region of the pulmonic conus, and the pulsations of the right auricle and the right ventricle are much reduced in amplitude. Angiocardiograms, as in valvular pulmonic stenosis, show delayed emptying of a large right auricle and ventricle, but the contrast solution can usually be seen to extend almost to the margin of the cardiac silhouette, indicating that the right auricle and right ventricle are thin-walled. Although cardiac catheterization is not recommended if the diagnosis of Ebstein's anomaly is suspected, in 1 patient in whom it was performed, the findings differed from those of valvular pulmonic stenosis in that the pressures in the right auricle and right ventricle were not greatly elevated.[20]

Cor pulmonale with patency of the foramen ovale[21] may be confused with this malformation. The quality of the second sound at the base may aid in the differentiation of these two malformations. In patients with pulmonic stenosis, the second sound at the base is weak, whereas in cor pulmonale it is usually accentuated. In doubtful instances cardiac catheterization and measurement of the pressure in the pulmonary artery may be necessary to differentiate the two conditions.

The Eisenmenger complex may be suggested by the delay in onset of cyanosis and the full pulmonary conus. The chief differential points in this malformation are the absence of a pulsating liver, the frequent finding of a blowing, diastolic murmur, and the fluoroscopic visualization of enlarged and pulsating pulmonary arteries and congested lung vascular markings. Due to the overriding aorta there is a short circulation time. The exercise test usually shows a rise in oxygen consumption per liter of ventilation after exercise. Right heart catheterization shows a high pressure in the pulmonary arteries as well as in the right ventricle.[22] It may be possible to catheterize the aorta from the right ventricle. On the angiocardiogram there is prompt emptying of the right side of the heart, the pulmonary circulation is increased, and there is early visualization of the overriding aorta.

SUMMARY

Three illustrative cases of valvular pulmonic stenosis with patency of the foramen ovale proved by autopsy have been presented. Although the malformation has been recognized at postmortem examination for the past 140 years, the correct diagnosis heretofore was rarely made before death. Nevertheless, correlation of the clinical and pathologic findings in the group of patients collected from the literature and of those which we have studied reveals that the clinical picture presented by this malformation is so characteristic as to permit its accurate diagnosis during life.

The salient features of the clinical syndrome are: delayed onset of cyanosis, dyspnea which is usually greater in severity and earlier in appearance than is the cyanosis, absence of squatting to rest after easy fatigue, a precordial bulge, an enlarged heart with a pulmonic systolic murmur and a weak second sound, and an enlarged and pulsating liver. Fluoroscopy shows vigorous pulsations in the enlarged right auricle and, unless it is failing, in the large right ventricle. The pulmonic conus is prominent, and there are large pulmonary arteries with minimal or absent expansile pulsations. The peripheral lung fields are abnormally clear. The electrocardiogram shows evidence of either right bundle branch block or right axis deviation and right ventricular hypertrophy. There is often a first degree A-V heart block and the P waves are high and peaked. The circulation time is usually prolonged. There is arterial oxygen unsaturation and compensatory polycythemia. Angiocardiogram shows delayed emptying of the hypertrophied right auricle and right ventricle and the dilated pulmonary artery; visualization of the aorta early in the series of films occurs only after some of the contrast solution has passed from the right auricle into the left auricle and left ventricle. Right heart catheterization shows an elevated pressure in the right auricle and right ventricle and a low pressure in the pulmonary artery.

The malformation must be differentiated from the tetralogy of Fallot, from Ebstein's anomaly of the tricuspid valve, from cor pulmonale, and also from the Eisenmenger complex. The differential diagnosis is discussed. It is important to make the correct diagnosis, for patients with this malformation may be helped by valvulotomy.

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A Hypertensive Syndrome with Relative Adrenal Cortical Overactivity

By DEAN F. DAVIES, PH.D., M.D., AND HELEN E. CLARK, M.D.

The authors have used the concentration of salt in sweat as an objective test to demonstrate the existence of a group of hypertensive patients with clinical signs of hyperadrenocortical function. The significantly lower concentration of salt in the sweat of patients with this endocrine hypertensive syndrome distinguishes them from other hypertensive patients who show no significant difference from normal. That this difference reflects an adrenal pathway is further suggested by Conn's demonstration that hypoadrenal activity is associated with high concentrations, and hyperadrenal function with low concentrations of salt in sweat.

IT HAS BEEN repeatedly demonstrated in the treatment of Addison's disease,[1–3] in rats,[4–7] and in normotensive and hypertensive human beings[8–10] that desoxycorticosterone acetate in large enough doses will elevate blood pressure to pathologic levels. Although many suggestions have been made that the adrenal cortex may play a role in the causation of human essential hypertension[9–15] there is no sound evidence that cases so classified have hyperactivity of adrenal cortical function.

Recently, Conn[16–19] has used a method of estimating the salt-retaining function of the adrenal cortex by measuring the concentration of salt in sweat. He found sodium and chloride concentrations high in Addison's disease and very low in Cushing's syndrome. Schroeder[20–23] has pointed out some of the clinical characteristics of a group of hypertensive women which he tentatively called "pseudo-Cushing's syndrome." This group has been differentiated chemically as well as clinically from other types of "essential" hypertension and will be shown to have the abnormal salt concentration of sweat characteristic of hyperadrenocorticalism. The majority of cases of hypertension of other, or unknown, etiology do not have this characteristic.

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A preliminary report of this work has been presented before the Fall Meeting of the American Physiological Society, Augusta, Georgia, September, 1949.

METHODS

Selection of Subjects

Controls. Subjects included in this report fell into four groups. Twenty-one normal, active members of the hospital staff, most of whom were in their third decade, served as controls. Ten were men; 11 were women.

*Endocrine Hypertensive Syndrome.** A second group of 24 hypertensive women were selected for evidence of metabolic disturbances of the type which has been tentatively called "pseudo-Cushing's syndrome."[21] The three most important diagnostic clinical findings in these patients were: central obesity, which was often excessive, chiefly in the thighs, abdomen, breasts and face; a history of sudden weight gain, often occurring at the menarche, menopause, after childbirth or after gynecologic operation; and menstrual abnormalities, including artificial menopause. Secondary and less common signs included hirsutism, light striae on abdomen and thighs and occasionally on upper arms, tendency to bruise easily and the presence of sugar in the urine or a diabetic type of glucose tolerance curve. Table 4 shows a tabulation of the presence or absence of each of these signs.

Other Hypertensives. A third group consisted of 16 hypertensive women and 6 hypertensive men. None of them had enough characteristics of the

* This nonspecific term is used in preference to one referring to the adrenal cortex, because the possibility remains that the clinical and laboratory manifestations of hyperadrenocortical activity are relative and due to a decrease in some balancing hormone. It seems more likely that stimulation of the adrenal cortex is part of a chain of endocrine disturbances which may involve the ovary and the pituitary.

endocrine syndrome to warrant the diagnosis. One had coarctation of the aorta, 2 chronic glomerulonephritis, and the other 19 had hypertension of unknown etiology (Table 5).

110 F. as near saturation as possible. At the end of 15 minutes and at the end of 30 minutes, sweat was collected directly into a chemically clean test tube from the cleaned area. During this interval internal

TABLE 1.—*Sweat Sodium and Chloride Concentrations in Normal Men and Women*

Subject	No. of Tests	Age	Race	Sweat Sodium		Sweat Chloride		MnNa/Mn Cl
				15 Min.	30 Min.	15 Min.	30 Min.	
				Men				
				mEq/l.	*mEq/l.*	*mEq/l.*	*mEq/l.*	
D. D.	4	31	W	39.0	60.3	36.8	61.0	1.01
A. W.	1	31	W	92.9	90.3	80.0	97.8	1.03
H. S.	1	43	W	70.0	77.8	62.2	70.6	1.11
V. T.	1	26	W	42.5	36.2	33.8	39.8	1.07
S. J.	1	23	W	53.7	58.4	56.0	69.6	0.89
O. R.	1	22	N	69.6	84.2	73.6	92.0	0.92
D. L.	1	23	W	95.5	100.0	98.0	102.4	0.98
R. J.	1	21	W	44.6	50.4	41.8	52.0	1.01
A. K.	1	32	W	88.6	87.5	90.2	89.6	0.98
J. N.	2	24	W	26.7	45.5	22.0	42.3	1.12
A. G.*	1	24	W	19.6	21.8	27.8	19.2	0.88
Means				58.4	64.8	56.6	66.9	1.00
σ				15.1	25.9	25.9	25.7	0.08
σ_{Mn}				8.0	7.5	7.5	7.8	0.02
				Women				
E. M.	1	26	W	47.5	70.0	50.4	52.2	1.14
G. G.	1	22	W	42.7	74.5	38.0	40.0	1.50
B. W.	1	23	W	66.8	64.1	55.6	66.5	1.07
W. B.	1	22	W	19.4	44.7	21.4	61.4	0.77
H. H.	1	25	W	92.6	—	93.8	—	—
T. K.*	1	28	W	68.3	70.2	84.6	81.2	0.84
J. S.	1	19	W	—	64.5	—	92.0	—
J. F.	1	22	W	33.3	45.5	37.6	53.5	0.87
J. G.	1	23	W	16.8	42.5	39.0	37.1	0.78
H. C.†	1	25	W	38.5	54.0	38.6	53.8	1.00
M. C.	1	22	W	42.4	41.3	—	46.0	—
Means				46.8	57.1	45.7	55.7	1.00
σ				22.1	12.3	13.8	16.5	0.20
σ_{Mn}				7.4	4.1	4.9	5.5	0.08

* Three months pregnant.
† Summer. Others in winter.

Obesity. Eight normotensive women were selected for obesity alone to rule out any role this factor might play in the endocrine group Schroeder described, since the maximum weight of the patients of the latter group averaged over 200 pounds.

Technic

The entire back of each subject was sponged clean with alcohol and dried. The subject was permitted to sit in a steam room maintained between 102 and

body temperatures rose considerably. The possibility of condensation of moisture on the skin as well as of evaporation from the body, though not completely eliminated, were thought to be negligible. However, because of the greater possibility of condensation of moisture on the skin at the beginning and because of the probability that full response to the sweating stimulus was not acquired as rapidly in one subject as in the next, the 30 minute samples were taken as the more dependable. The greater

range of concentrations in the 15 minute samples of each group is in keeping with this reasoning.

Analyses for sodium were made on the Beckman Flame Photometer at a wave length of 589 μ and for chloride by titration, using the Wilson-Ball modification of the Van Slyke method.[24] Statistical analysis for the significance of differences between means was made by Fisher's t test for small samples[25] from which probability values were found.

Season. Table 2 shows a comparison of tests performed on the same normal subjects between February and August. Salt concentrations in sweat were found to fall with seasonal increases in temperature. In February, when the average St. Louis temperature was 35.8 F., the mean concentration of sodium in the 30 minute

TABLE 2.—*Sweat Sodium and Chloride Concentrations in Winter and Summer on Same Subjects*

Subject & Sex	Date	Sweat Sodium		Sweat Chloride		Na/Cl	
		15 Min.	30 Min.	15 Min.	30 Min.	15 Min.	30 Min.
				Winter			
E. M.♀	2/18/49	47.5	70.0	50.4	52.2	0.94	1.34
G. G.♀	2/18/49	42.7	74.5	38.0	40.0	1.12	1.86
B. W.♀	2/18/49	66.8	64.1	55.6	66.5	1.20	0.96
W. B.♀	2/18/49	19.4	44.7	(21.4)*	61.4	(0.91)*	0.73
H. H.♀	2/19/49	92.6	—	93.8	—	0.99	—
D. D.♂	†	39.0	60.3	36.8	61.0	1.06	0.99
H. S.♂	2/18/49	70.0	77.8	62.2	70.6	1.12	1.10
Mean		54.0	65.2	56.13	58.6	1.07	1.16
				Summer			
E. M.	7/26/49	20.2	14.6	15.6	18.5	1.29	0.79
G. G.	7/26/49	34.0	39.5	33.0	38.0	1.03	1.04
B. W.	7/26/49	44.0	49.1	34.8	47.8	1.26	1.03
W. B.	7/26/49	31.4	33.3	—	27.0	—	1.23
H. H.	7/26/49	19.3	(19.9)*	13.8	(14.2)*	1.40	(1.40)*
D. D.	7/26/49	32.0	41.6	25.6	33.2	1.25	1.25
H. S.	7/26/49	44.8	57.0	42.0	54.2	1.07	1.05
Mean		32.2	39.2	27.5	36.5	1.21	1.07

* Parenthesis around figures indicates they were not included in means.
† Mean of 4 tests: 2/14/49, 2/18/49, 2/19/49, 2/23/49.

RESULTS

Sex. Table 1 shows concentrations of sodium and chloride in sweat in milliequivalents per liter in normal men and normal women after 15 and 30 minutes in the steam room. Tests were done in the winter in all but one man and one woman so that the effect of seasonal variation is not present. Although the mean values for both sodium and chloride are lower in women than in men, the individual variation is so great in both groups that the differences are not significant. However, it is possible that women could be shown to average lower sweat salt concentrations than men by a much larger sampling.

samples of sweat was 65.2 mEq. per liter. In July, the mean temperature was 80.8 F. and the sodium concentration in sweat of these subjects averaged 39.2 mEq. per liter. The average decrease in sodium concentration in these subjects compared favorably with the differences found between two groups of 19 summer and 19 winter tests on normal subjects (fig. 1) including those in table 2. The mean 30 minute sample had a sodium concentration of 30.7 mEq. per liter lower in summer than in winter.

Since patients were tested in each month from February to August, this seasonal variation had to be taken into consideration in

comparing groups with each other. Of the 24 endocrine hypertensive patients 10 were tested in winter. The other 14 patients were tested between June 29 and August 10. Among the nonendocrine hypertensives, 7 of 22 patients were tested in summer.

Weight. Since one of the clinical characteristics of Schroeder's endocrine syndrome is obesity, the 8 normotensive obese women given the test were compared with 8 normotensive women of normal weight. The results are shown in table 3. The mean weight of the obese group was 194 pounds, while the others averaged 122 pounds. Obesity, per se, did not consistently alter salt excretion in sweat. Actually the range of concentrations was much larger among the

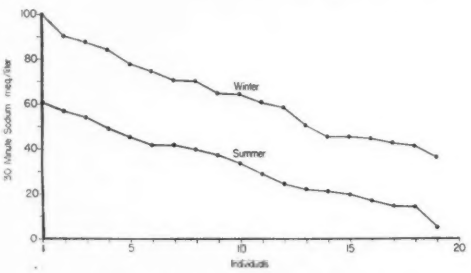

FIG. 1. Seasonal differences in electrolyte concentration of sweat between two groups of normal subjects. Points represent individual sodium concentrations arranged in descending order for each group.

obese women than among the normals, but there was no significant difference in either the 15 or 30 minute samples between the two groups. Because of this lack of difference and since the obese normotensives were tested in summer they were incorporated into the summer group of figure 1.

Hypertension. Only 3 of the 24 endocrine hypertensive patients had a concentration of sodium in sweat above 35 mEq. per liter at 30 minutes. In one it was 38.3 and was the only sample obtainable. Although rates of sweating were not measured, difficulty in obtaining sweat from the back was found fairly frequently in this group of patients. The mean of the sodium concentration at 30 minutes for the entire group of the endocrine syndrome was 20.2 mEq. per liter. These results are shown in table 4.

Of the 22 cases of other types of hypertension (table 5), only 4 had concentrations of sodium in sweat collected at the end of 30 minutes below 35 mEq. per liter. One (F. Wal.) was a man with nephritis, one (J. Ros.) an overweight man with neurasthenic symptoms, one a markedly underweight woman of 33 (A. She.), and one (A. Kno.) a woman with a history of menstrual abnormalities but no other signs of endocrine dysfunction. The mean sodium concentration at 30 minutes for the entire group

TABLE 3.—*Obese Normotensive Women—Summer*

Patient	Race	Age	Wt.	Sweat Sodium	
				15 Min.	30 Min.
Dol., J.	W	38	201	29.7	24.2
Bro., M.	N	58	199	120.0	60.8
Gat., O.	N	23	175	13.0	5.0
Mer., D.	W	30	178	18.2	21.0
Wil., L.	W	37	179	25.2	37.1
Joh., E.	N	39	228	18.6	16.9
Wat., F.	W	40	177	21.2	45.1
Jen., V.	N	27	215	35.9	14.3
Mean		36.5	194	35.2	28.1
σ				32.7	17.2
σ_{Mn}				12.4	6.5
Normal Weight Normotensive Women—Summer					
Men., E.	W	26	103	20.2	14.6
Gol., G.	W	22	125	34.0	39.5
Whe., B.	W	23	105	44.0	49.1
Bru., W.	W	22	135	31.4	33.3
Hil., H.	W	25	110	19.3	19.9
Cha., H.	W	25	130	38.5	54.0
Lan., B.	W	23	140	29.0	28.9
Mue., D.	W	28	125	32.9	41.6
Mean		24.3	122	31.2	35.1
σ				24.9	12.8
σ_{Mn}				9.4	4.8

was 51.5 mEq. per liter. Six men were included in this group. The mean of their concentrations of sweat sodium was lower than that of nonendocrine hypertensive women; their inclusion therefore decreased the differences between endocrine and nonendocrine groups.

Known Duration and Severity of Hypertension. In the endocrine series the known duration of hypertension varied from one month to 16 years, the mean being 4.3 years. Six had been recognized less than one year. The duration of

hypertension in the others varied from 6 months to 18 years and averaged 7.8 years While it might be argued on this basis that the type described by Schroeder represents an early stage of hypertension, the absence of any history of the signs and symptoms discussed above in the group of unknown etiology is fairly conclusive evidence against this possibility. Comparison of the highest recorded diastolic blood pressures of each patient showed that the distribution of mild (<100 mm. Hg), moderate (100–120 mm. Hg) and severe (>120 mm. Hg) levels was approximately equal in the two groups. Eleven patients in each group fell in the severe category; 2 with the endocrine hypertensive syndrome and 4 of the others were mild. When the groups were divided into mild, moderate and severe categories according to the lowest recorded diastolic pressures, the distribution was 10, 10 and 4 for the endocrine type and 9, 11 and 2 for the others, respectively.

TABLE 4.—*Endocrine Hypertensive Syndrome*

Patient	Date	Sex	Race	Age	Sweat Sodium		Maximum Weight	Present Weight	Known Duration of Hypertension	Central Obesity	Sudden Weight Gain	Menstrual Abnormalities	Hirsutism	Light Striae	Easy Bruising	Diabetic Glucose Tolerance Curve	Urine Sugar
					15 Min.	30 Min.											
							Lbs.	*Lbs.*	*Yrs.*								
Sca., M.	3/23/49	♀	N	49	8.0	8.9	183	169	2	+	+	+	0	0	+	0	+
Smi., L.	2/22/49	♀	W	43	44.7	53.1	216	170	8	+	0	+	+	+	+	+	0
Tat., M.	4/27/49	♀	N	39	19.1	19.6	212	206	4	+	+	+	0	+	0		0
Cha , L.	*	♀	N	34	9.2	5.8	291	204	8	+	0	+	+	+	0	0	0
Lar., M.	†	♀	W	47	21.9	22.1	210	162	3	+	+	0	0	+	0	+	0
Bla., H.‡	2/21/49	♀	W	29	—	29.8	285	200	8	+		+	0	+		+	0
Mon., S.	§	♀	N	58	29.5	23.5	189	140	6	+	+	+	0	+	+		0
Ray., F.	7/20/49	♀	W	40	35.5	19.7	194	179	$\frac{5}{6}$	+	+	+	0	+	0		+
Kec., I.	7/13/49	♀	W	40	22.5	18.7	161	140	3	+	+	0	0	+	+		0
Pru., M.	7/21/49	♀	W	29	14.8	21.6	173	145	$\frac{3}{4}$	+	+	+	+		+	0	0
Ruc., E.	7/20/49	♀	N	41	12.6	9.4	205	163	6	+	+	+	0	+	+		+
Pru., L.	7/13/49	♀	N	42	3.3	3.3	175	171	$\frac{1}{6}$	+	0	+	0	+	0		0
Hen., O.	7/27/49	♀	N	50	7.7	7.2	162	159	$1\frac{1}{4}$	+	+	+	+	+	0		0
Hud., G.	8/10/49	♀	N	37	10.0	10.5	225	207	2	+	0	+	+	+	0		0
Cud., M.	3/30/49	♀	W	43	24.3	22.5	300	160	16	+		+	0	+	0	0	0
Hin., M.	7/27/49	♀	W	44	12.8	9.8	250	—	10	+	+	0	0	+	0		0
Lon., M.	6/29/49	♀	W	44	11.8	18.4	200	156	1	+	+	+	0	+	+		+
Mil., L.	7/20/49	♀	W	51	86.9	58.9	165	—	—	+	+	0	0	+	+		0
Sto., M.	3/5/49	♀	W	34	28.1	34.7	160	125	10	+	+	+	0		+		0
Spe., L.‡	2/22/49	♀	W	47	—	38.3	276	150	1	+		0	0	+			0
Mar., R.	8/10/49	♀	W	58	18.5	25.1	260	249	2 wks.	+		0	+	+	0		0
Wil., A.	8/10/49	♀	N	39	7.5	9.4	197	177	1	+	0	+	+	+	0	+	+
Spe., H.	8/10/49	♀	N	57	10.7	9.1	235	219	6	+	+	+	+	0	+		0
Ste., A.	8/8/49	♀	N	38	13.4	4.9	256	125	$\frac{1}{12}$	0	+	+	+	+	+		
Means					20.6	20.2											
σ					17.6	13.9											
σ_{Mn}					3.8	2.9											

* Mean of tests on 2/25, 3/5, 3/31/49.
† Mean of tests on 2/21, 3/11, 5/24, 6/1/49.
‡ 45 minute sample.
§ Mean of tests on 2/23, 3/8, 5/11/49.

Sodium to Chloride Ratio. The ratio of sodium to chloride* concentrations in the 15 and 30

* In making these comparisons chloride values below 5.0 mEq. per liter were rejected because of the titrimetric error in determining such small amounts.

TABLE 5.—*Other Types of Hypertensives*

Patient	Date	Sex	R	Age	Cl. Dx	Sweat Sodium		Maximum Weight	Present Weight	Known Duration of Hypertension	Central Obesity	Sudden Weight Gain	Menstrual Abnormalities	Hirsutism	Light Striae	Easy Bruising	Diabetic Glucose Tolerance Curve	Urine Sugar
						15 Min.	30 Min.											
								Lbs.	*Lbs.*	*Yrs.*								
Pon, C.*	6/ 2/49	♀	W	60	ess. hyper.	74.9	45.0	130	130	10	0	0	0	0	0	+		0
McC., W.	†	♂	W	51	ess. hyper.	49.4	50.4	170	150	1	0	0	−	−	0	+		0
Ber., B.	‡	♂	W	23	glomerulonephritis	38.9	44.8	156	140	11	0	0	−	−	0			+
Wil., J.	2/16/49	♀	W	45	ess. hyper.	70.4	56.7	144	129	8	0	0	+	+	+	0		0
Per., I.	5/ 6/49	♀	N	41	ess. hyper.	70.8	56.2	172	149	15	+	0	0	0	+			0
Phi., M.	§	♀	N	46	ess. hyper.	36.8	46.0	174	156	2	0	0	0	0	+	+	0	0
Cri:, S.	7/20/49	♀	W	46	ess. hyper.	57.8	69.3	179	162	11	+	0	0	0	+	0		0
Kno., A.	3/26/49	♀	N	48	ess. hyper.	11.9	9.6	134	132	18	0	0	+					0
Ros., J.	3/ 8/49	♂	W	51	ess. hyper.	27.2	23.6	176	159	?	0	0	−	−	0	0		0
Hoe., M.	2/23/49	♀	W	48	ess. hyper.	63.6	—	100	91	17	0	0	+	0	0	0		0
Sve., M.	2/21/49	♀	W	36	ess. hyper.	41.8	39.0	170	138	4	0	0	0	0				0
Mal., C.*	2/23/49	♂	N	40	ess. hyper.	55.4	90.3	199	168	9	0	—	−	−	0	0		0
Jus., V.	2/ 9/49	♀	W	34	coarctation of aorta	63.6	85.0	125	—	3	0	0						0
Mos., R.	2/18/49	♀	W	47	ess. hyper.	41.7	67.1	—	"thin"	7	0	0	0	0	0	0		0
Joh., M.	2/23/49	♀	W	31	ess. hyper.	65.7	71.5	113	102	7	0	0	+	0	0			0
Wal., F.	2/14/49	♂	W	31	glomerulonephritis	38.4	28.0	—	—	—	0	0	−	−	0	0		0
She., A.	8/10/49	♀	N	33	ess. hyper.	19.2	19.6	105	90	2	0	0	0	0	0	0		0
Sha., S.	3/ 2/49	♀	W	48	ess. hyper.	80.1	75.6	134	132	3	0	0	+	0	0			0
Tra., S.	5/25/49	♀	N	43	ess. hyper.	54.3	56.5	141	118	8	0	0	+	0	0	+	0	0
O'S., K.	2/23/49	♀	W	55	ess. hyper.	47.7	52.8	170	142	17	+	+	0	0	+	0		+
Mil., R.	2/23/49	♂	W	23	ess. hyper.	49.7	57.3	179	177	½	0	0	−	−	0	0	0	0
Tho., L.	8/ 6/49	♀	N	41	ess. hyper.	50.4	37.5	265	207	3	0	0	0	0	+	+		
Mean						50.4	51.5											
σ						17.3	20.5											
σ_{Mn}						3.8	4.6											
♂ mean						43.1	47.5											

* 30 and 45 minute samples respectively.
† Mean values of tests on 2/18/49 and 2/25/49.
‡ Mean values of tests on 3/2/49 and 5/4/49.
§ Mean values of tests on 2/16/49, 5/4/49 and 6/1/49.

minute samples were calculated. The average values of both samples were 1.0 for normal men and for normal women in winter (table 1). There were differences between the two samples

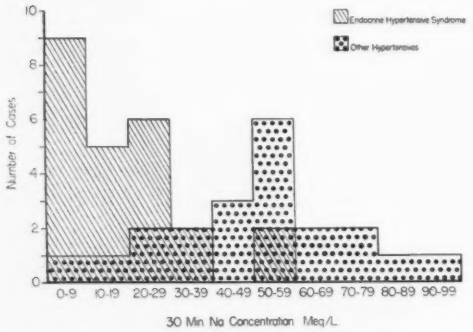

FIG. 2. Frequency histograms comparing sodium concentrations of sweat after 30 minutes in a steam room in two groups of hypertensive subjects.

ANALYSIS

Figure 2 shows a comparison of the two hypertensive groups uncorrected for seasonal differences. The data fall into two distinct distribution curves. As might be suspected, the concentrations of sodium in sweat of some of the patients with the endocrine hypertensive syndrome are not as low as is found in Cushing's syndrome.

Table 6 shows probabilities that the differences between various groups could be explained by chance. The difference between normal men and women and between normal-weight normotensive women and obese normotensive women is not significant. On the other hand, the difference between winter-normal and summer-normal tests is highly significant. To establish the fact that the endocrine hypertensives have lower concentrations of salt in

TABLE 6.—*Significance of Differences Between Groups*
(30 minute sweat sodium concentration)

Group	Mean	t	p	D.F.	Mean	Group
	mEq/l.				*mEq/l.*	
Normal men	64.8	0.90	>0.30	19	57.1	Normal women
Normal women*	35.1	0.87	>0.30	12	28.1	Obese women*
Winter normals	63.6	5.4	<0.001	16	32.9	Summer normals
Endocrine hypertensive syndrome	20.4	2.6	0.01	41	32.9	Summer normals
Other hypertensives	51.5	1.9	0.07	39	63.6	Winter normals
Other hypertensives (summer)	44.8	1.3	0.20	22	56.1	Other hypertensives (winter)

* Summer only.

and between winter and summer determinations. The effect of season seemed real; while the ratio fell 14 per cent in normal subjects (table 2) in summer, the same individuals showed an average increase of 9 per cent in winter. The winter tests of both hypertensive groups showed a tendency for the ratio to decrease in the 30 minute sample. The endocrine group showed an average change in ratio of sodium to chloride from 1.19 to 0.96, a fall of 23 per cent, and the nonendocrine hypertensives an average decrease of 14 per cent (1.19 to 1.03). Although these differences cannot be adequately interpreted, they show that sweat sodium and chloride values have generally the same order of magnitude.

sweat than other groups, they were compared with summer-normals in spite of the presence of 10 who had tests in winter, thus tending to raise the mean and the standard deviation of the group. In spite of this there is 1 chance in 100 that it is not a statistically distinct group.

These differences were obtained without consideration for the physiologic state of the patients except that those who had been on low salt diets were instructed to take salt *ad libitum*. Tests on patients who remained on low salt diets were not used in these studies. The effect of a meal, of exercise, of emotional states or time of day were not investigated. None were basal. It is probable that the differences demon-

trated would be even more significant if variations due to these factors were controlled.

Similarly, the other hypertensives were compared with the highest (winter) normal group, in spite of the presence of 8 summer-hypertensive patients, to see if hyperadrenocortical function could be claimed. The chances that they belong to the same group are over 35 in 100 in spite of the presence of two cases of glomerulonephritis which tended to increase the difference between the groups.

Figure 3 shows mean 30 minute sodium values of normals, and endocrine and other hypertensives in winter and summer. It is seen that the normals and endocrine hypertensives decrease almost 50 per cent in summer. The

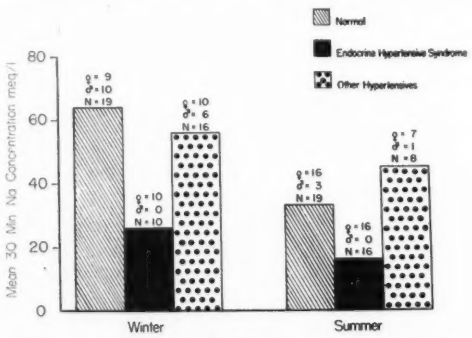

FIG. 3. Mean seasonal differences in concentration of sodium in sweat for normal subjects, patients with endocrine and nonendocrine hypertension. See text.

change in the other hypertensives is not as great and is probably significantly less than the normals since the fall was only 20 per cent of the winter level; because of the small number of summer-hypertensives in this group the decrease is not statistically significant. Nor is the difference between summer-normals and summer-hypertensives significant.

DISCUSSION

Various descriptions of hypertensive states with an endocrine factor have been made. In some there are distinct differences from the characteristics of the endocrine hypertensive syndrome. Others, though poorly defined, are compatible with this diagnosis.

Cushing's syndrome[26] in women is characterized by hypertension, glycosuria, osteoporosis, obesity of the face and trunk, purple striae, hirsutism and amenorrhea. This symptom-complex has been explained on the basis of adrenal cortical tumors, lesions of the hypothalamus, adenomas and hyalinization of basophil cells of the pituitary, and tumors of the thymus. Cases of the endocrine type often qualitatively resemble Cushing's syndrome in a number of respects, including hypertension, central obesity, menstrual abnormalities, and low salt concentration in sweat. However, in general it is a milder and less easily recognized group of symptoms and may have no evidence of hirsutism, abnormal carbohydrate metabolism, or osteoporosis. In response to small doses of insulin, four showed increased ($>2\sigma_{Mn}$) and five showed decreased ($<2\ \sigma_{Mn}$) sensitivity. One fell within normal limits.[27] That it is clinically recognizable with few exceptions has been demonstrated by the confirmatory evidence of low salt concentration in sweat shown above.* It is probable that the cases studied, with the possible exception of L. Cha., result from hormonal imbalance without adenomatous growth.

One of the endocrine hypertensives, M. Lar., was studied in detail by Daughaday and MacBryde. On changing suddenly from a sodium intake of 3 mEq. per day to 205 mEq. per day "there was a remarkable carry-over of sodium conservation which produced a sodium retention far in excess of any possible deficit accrued by sodium restriction." However, salt intake had no effect on either 17-ketosteroids or formaldehydogenic steroid excretion. Two normo-

* It is not known whether these differences in salt concentration of sweat are due to differences in physiologic response to the stress stimulus of a steam room or to a pre-existing difference in the composition of sweat. However, a test for sodium in sweat reported recently by Leslie and Levin[28] in which only one arm was warmed, sweat being collected from the other arm, gave normal values no higher than ours. Unfortunately, they did not record the climatic conditions at the time the tests were done. However, it is apparent that a stress applied to one extremity has no less effect on the factors regulating retention of salt than one applied systemically. In either case there is no evidence for or against the adrenal cortex playing an etiologic role in the "endocrine hypertensive syndrome." However, the stimulation of adrenocorticotropic hormone by epinephrine must be considered as one possible mechanism.

tensive women accommodated rapidly to similar sudden increases in sodium intake by increases in sodium excretion. No effect on steroid excretion was observed in either patient. Another patient from our endocrine hypertensive group, L. Spe., had an abnormally high excretion of formaldehydogenic steroids.[29] Administered adrenocorticotropic hormone (ACTH) was active in stimulating sodium retriction, but extreme changes in sodium intake apparently have no noticeable effect on release of ACTH. The problems raised by these results have been well summarized by Perera.[30]

In 1941 Rinehart[31] added to the body of evidence that adrenal hyperplasia occurs often in cases of essential hypertension. Raab[32] in the same year reviewed the evidence for the part played by the adrenal in hypertension and demonstrated an increase in adrenocortical substances in the blood in cases of "renal" hypertension with and without renal insufficiency as well as in congestive heart failure. He found no clear relation between the blood level of adrenocortical compounds and the blood pressure and concluded that these compounds further the development of arteriolosclerosis with secondary ischemic effects on the vasomotor centers of the brain and in the kidneys.

The endocrine hypertensives reported here are not characterized by any degree of renal impairment and are occasionally mild cases with few symptoms. They cannot be called "renal" hypertensives since positive evidence for a renal factor is lacking. Usually intravenous pyelography and urine cultures are negative. Therefore, we do not believe this group is related to the type Raab has reported.

Bruger and co-workers[33] confirmed previous reports that hypertension "is not necessarily accompanied by any specific alteration in the histology of the adrenal cortex." They further reported a lower 17-ketosteroid excretion in hypertensive than in normal subjects. These findings are not incompatible with our results.

F. Selye[12] reported the serum sodium to chloride ratio in 10 hypertensive patients to be elevated above 1.44, whereas in 24 other hypertensives and all normal subjects the ratio fell below this level. Although sweat sodium to chloride ratios were not elevated in the endocrine group, some of her cases may have fallen into this category.

Heinbecker[14, 34] has used studies of Cushing's syndrome "as a basis for a concept of the pathogenesis of essential hypertension because in both states there invariably develops diastolic hypertension and arteriolar sclerosis." It may be that this analogy can be applied to the endocrine hypertensive syndrome, but evidence for hyperadrenocortical function in the remainder of essential hypertensives is still lacking. The acclimatization of our other hypertensives to a St. Louis summer as measured by changes in sweat salt concentration seemed to be less than that of the normal and endocrine subjects (fig. 3). Although this requires confirmation, it would suggest depletion of adrenocortical reserves. That blood pressure can be maintained at high levels with normal or decreased function of the salt-retaining factors in such individuals is taken as indirect evidence that such a mechanism does not play a prominent role in the maintenance of their hypertension.

H. Selye and associates[35] have recently reemphasized their previous evidence that the production of hypertension and nephrosclerosis in rats is dependent on administration of *both* desoxycorticosterone *and* the sodium ion. Neither DCA and a salt-free diet nor 1 per cent sodium chloride without DCA resulted in nephrosclerosis or a significant change in blood pressure. These data are particularly pertinent in the light of Schroeder's report of patients falling into this clinical syndrome who responded to a low salt diet by a fall of blood pressure.[21] Other hypertensives did not respond to a low salt diet with a significant fall in blood pressure. Four of those who did respond have since been found to have low sweat salt concentrations. Similar results have been obtained by Grollman and associates.[36] Sensitivity of blood pressure to sodium chloride intake was found in 2. All three who responded were women; one had had an operation for removal of uterine myomas, and a second was obese. These facts suggest that the differences in response to salt restriction found may have been related to the type of hypertension which these patients had.

Although the electrolyte-regulating zona

glomerulosa of the adrenal cortex seems to be relatively unaffected by hypophysectomy in the rat,[37] there is good evidence that adrenocorticotropic hormone influences electrolyte metabolism in man. There is an increased salt retention after administration of adrenocorticotropic hormone (ACTH),[38] presumably a manifestation of increased adrenocortical function. Decreased concentration of salt in sweat has also been found by Conn and ourselves after ACTH administration[18, 29] and in acclimatization to heat.[17, 19] The effect of changes in climatic conditions on adrenal cortical function has been studied by Kark.[39] Sudden exposure to cold produced metabolic changes, including sodium and chloride retention, similar to those following the injection of adrenocorticotropic hormone. This link would make a primary disturbance in the cerebral cortex or hypothalamus more plausible by permitting a pituitary-adrenal pathway for the production of the symptomatology characteristic of increased adrenocortical function. However, other possible explanations of the defect in the syndrome here described include suppression of the inhibiting effect of ovarian hormones on the pituitary by decreased ovarian function as suggested by the gynecologic history. There may also be a true or relative decrease in production of a salt-losing hormone. Investigation of the possibilities is in progress and detailed case studies of these patients will be published.

Conclusions

Hypertensive patients selected at random from the wards of Barnes Hospital and the Hypertension Clinic of Washington University have been separated into two groups, each with a distinct distribution curve of the concentration of sodium and chloride in sweat, and with dissimilar clinical characteristics. The results are presented as evidence (1) for the existence of a type of hypertension in which there is an abnormal reabsorption of salt from sweat probably mediated through the adrenal cortex, together with clinical signs of hyperadrenocortical function; (2) against a hyperactivity of the salt-retaining hormone of the adrenal cortex in the majority of cases of essential hypertension.

The proportion of hypertensives belonging to the endocrine hypertensive syndrome is greater than originally thought but probably does not exceed 20 per cent of all cases of essential hypertension.

Summary

1. Standards for normal men and women and obese women have been established for a test of salt concentration in sweat.

2. Differences between winter and summer for normal subjects under the conditions of the test have been established.

3. A new syndrome has been distinguished from the group previously called essential hypertension by clinical characteristics and by demonstration of a significant difference in their sweat salt concentrations.

4. The remainder of hypertensive patients studied were found not to differ from the normal group in their sweat salt concentration.

5. It is suggested that the salt retaining hormone of the adrenal cortex is not hyperactive in the majority of cases of hypertension, but that it may be in the new group identified by Schroeder.

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The Nature of Pressor Substances in Pheochromocytomas

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The actions of aqueous extracts of two pheochromocytomas are compared before and after the administration of the adrenergic blocking agent, Dibenamine. One tumor contained predominantly a substance which, like norepinephrine, had pressor actions after Dibenamine. The other tumor contained chiefly an epinephrine-like substance. The significance of the presence of norepinephrine in pheochromocytomas and its role in epinephrine metabolism are discussed.

SEVERAL investigators have detected norepinephrine in various tissues[1–6] and in Epinephrine, U.S.P., derived from the adrenal glands of cattle.[7–9] The suggestion has been made repeatedly that norepinephrine may be a chemical mediator at certain adrenergic neuroeffector junctions.[1, 6, 7, 10–13] There have appeared during the past year the first, and almost simultaneous, reports[7, 14, 15] of the presence of varying amounts of norepinephrine in the human adrenal medulla and in pheochromocytomas. In a preliminary paper,[16] published at virtually the same time, we reported the presence of a large amount of a "pressor substance other than epinephrine" in a pheochromocytoma. In each of these studies different chemical and biologic methods of identification were used. We have recently assayed a second pheochromocytoma. Methods similar to ours have been used by Beyer[17] in the study of two adrenal medullary tumors.

There were distinct differences in the clinical aspects of our two cases. The first tumor (hereafter referred to as tumor A) was removed from a 13 year old white boy who had severe sustained arterial hypertension. The clinical features resembled those seen in essential hypertension, and this emphasizes the necessity for considering pheochromocytoma in the differential diagnosis of arterial hypertension.

CASE REPORTS

Case 1. F. L., a 13 year old white boy, had complained of difficult vision for one year. He was examined by an ophthalmologist who noted changes in the ocular fundi compatible with those of an hypertensive retinopathy. He was referred to Doernbecher Memorial Hospital on Nov. 11, 1948. The only other symptoms were transient headaches associated with exertion, occasional episodes of sweating and intermittent pain in the lumbar region.

He was a ruddy complexioned, alert and well developed boy who appeared well. The arterial blood pressure measured in the arms was 212/154, the pulse rate was 120, full and regular. There was marked edema of the optic discs and in the posterior poles of the retina with numerous large white exudates and striate hemorrhages. There was generalized constriction of the retinal arteries with well marked segmentation. The left cardiac border was displaced slightly to the left; the second aortic and pulmonic sounds were loud and snapping. The remainder of the physical examination was negative.

Routine studies of the blood, urinalyses, phenolsulfonphthalein test for kidney function, dextrose tolerance test, electrocardiograms, intravenous pyelograms and laminograms of both kidney areas were normal.

On Nov. 15, 1948, N-piperidino-methyl-benzodioxane (20 mg.) was administered intravenously. Within two minutes after beginning the injection, the arterial blood pressure fell from 178/138 to 152/100 and then rose in the next 15 minutes to 198/158 mm. Hg. On Nov. 17, 1948, 2 mg. per Kg. of body weight of the adrenergic blocking agent, N,N dibenzyl beta-chloroethylamine (Dibenamine), was injected intravenously. The arterial blood pressure fell from the resting level of 228/174 to 184/144 three minutes after beginning the injection and had fallen to 130/100 six and one-half hours after Dibenamine where it remained for six hours (fig. 1). This result suggested that the major part of the patient's hypertension was due to circulating epinephrine or an epinephrine-like substance. On Nov. 18, 1948, under basal avertin anesthesia supplemented with nitrous oxide and oxygen, a tumor of the left adrenal gland weighing 28 Gm., was removed and identified histologically as a pheochromocytoma. Benzodioxane and Dibenamine injections postoperatively have produced no significant changes in the

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arterial blood pressure while the patient remained in the supine position. He was last seen in December, 1949, at which time he was asymptomatic and his arterial blood pressure was 132/88.

The second case (hereafter referred to as tumor B) exhibited the symptoms more commonly associated with pheochromocytomas.

*Case 2.** W. C., a 26 year old white rancher, was admitted to the Veterans Administration Hospital, Portland, Oregon, on Aug. 19, 1949. For one year he had noted frequent episodes of transient weakness, "knotting" in his stomach, palpitations, sweating and headache. These attacks were induced by activity and were relieved by rest. On one occasion the attack seemed to be related to emotional stress. He

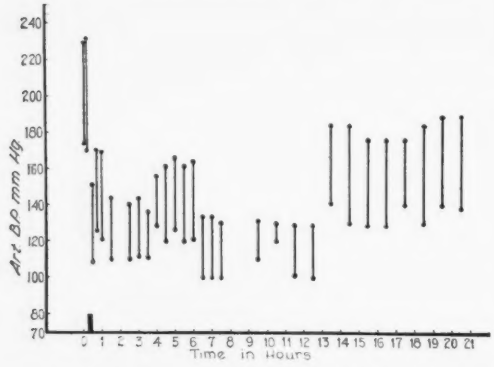

FIG. 1. The response of the arterial blood pressure of a 13 year old male with a pheochromocytoma to the injection of 2 mg. per Kg. of Dibenamine. Time of injection is indicated by thick vertical line. The patient remained supine throughout the test period. Time in hours.

was first seen at the Veterans Hospital as an outpatient. At that time his arterial blood pressure was reported to be within normal limits. The administration of 0.05 mg. of histamine base was followed by an elevation of the systolic blood pressure to 230 mm. Hg.

Physical examination revealed no abnormal findings. The arterial blood pressure was 120/80 mm. Hg.

Laboratory studies: Hematology, urinalyses and serology were normal. The fasting blood glucose was 145 mg. per 100 cubic centimeters. The basal metabolic rate was +4 per cent. The dextrose tolerance tests were within normal limits.

During "attacks" the arterial blood pressure was not observed to exceed 150–160/90–100. On Aug. 29, 1949, a tumor weighing 9 Gm. was removed from the area medial and adjacent to the right adrenal gland. The tumor was identified histologically as a pheochromocytoma.

* The complete case report will be published by Drs. Jarvis Gould and A. L. Mundal, Veterans Administration Hospital, Portland, Oregon.

METHODS

The method of bioassay for each tumor was as follows: The arterial blood pressure of mongrel dogs, anesthetized with sodium pentobarbital, was recorded directly by means of a mercury manometer. Within two hours following surgical removal of the pheochromocytomas, aqueous extracts of the ground tumor tissue were prepared in the proportions of 10 cc. of distilled water per 1 Gm. of tumor tissue. The brei was then filtered through number 2 filter paper. An estimation of the pressor activity of the tumor extract was obtained by comparison with l-epinephrine solution of known concentration (Parke-Davis & Co., Adrenalin Chloride). Dibenamine was then injected slowly intravenously during a 12 to 15 minute period. The initial assays of tumor A were done using a Dibenamine dose of 30 mg. per Kg. of body weight. A reduction of blood pressure was obviated in the subsequent assays by using a dose of 15 mg. per Kg. of Dibenamine. Thirty minutes or more after completion of Dibenamine administration, the tumor extracts and known concentrations of epinephrine were again injected.

RESULTS

(1) *Effects of the Tumor Extracts upon Arterial Blood Pressure.* The extract of tumor A had marked pressor potency prior to Dibenamine administration; the pressor potency of 0.03 cc. of the extract was approximately equal to 1.0 cc. of 1:100,000 l-epinephrine. Following 30 mg. per Kg. of Dibenamine, the pressor response produced by the tumor extract was undiminished compared with the response prior to Dibenamine. These results are illustrated in figure 2. Epinephrine produced the fall of blood pressure that is observed after Dibenamine, and the degree of fall in pressure was greater the larger the dose. Injections of the tumor extract repeated within a short period of time produced qualitatively and quantitatively similar pressor responses. This is illustrated in figure 3. Injection of the tumor ex-

tract into an unanesthetized dog with a Thiry fistula of the jejunum caused complete inhibition of intestinal motility. This is shown in figure 4. The pressor potency of the refrigerated extract and of a freshly prepared extract of the refrigerated specimen was somewhat reduced 24 hours later, and was almost absent by the fifth day.

Aqueous extracts of tumor B produced pressor responses prior to Dibenamine. An amount of 0.05 cc. of the extract was equivalent in pressor potency to 1.0 cc. of 1:50,000 epinephrine. Following 15 mg. per Kg. of Dibenamine, the tumor extract in dosages up to 0.2 cc. produced depressor responses similar to those caused by epinephrine.

Two groups of normal beef adrenal glands were assayed, each group consisting of the combined tissues of 6 glands. The adrenal glands of 2 normal dogs were assayed separately. The extracts of both types of tissues produced pressor responses before Dibenamine. Following Dibenamine there was, in every instance, either no pressor effect or a fall of blood pressure similar to that occurring after the injection of l-epinephrine.

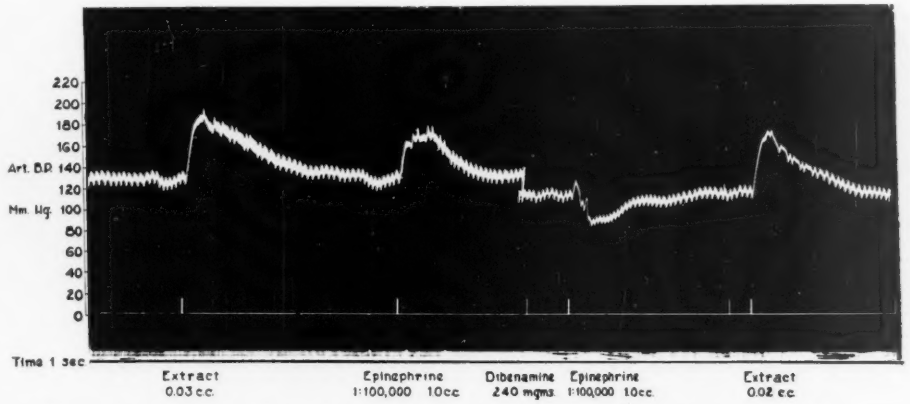

FIG. 2. Comparison of effects of extracts of tumor A and of epinephrine upon the blood pressure of a dog before and after the administration of 240 mg. per Kg. of Dibenamine (30 mg. per Kg.). At the third mark, the drum remained stationary for approximately 45 minutes.

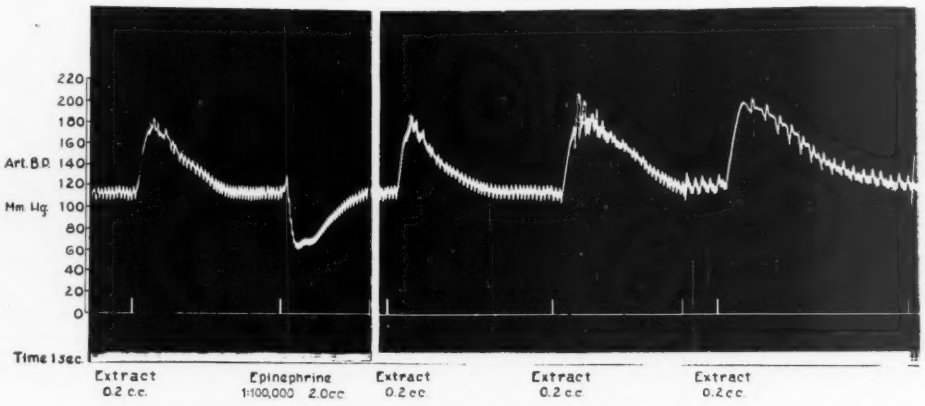

FIG. 3. A continuation of the record shown in figure 2, illustrating the undiminished effect of repeated injections of the extract.

The pressor responses produced by the tumor extracts may be attributed to a substance or substances either of sympathomimetic or nonsympathomimetic nature. The use of Dibenamine to differentiate these two classes of compounds rests upon its ability to block the pressor activity of sympathomimetic compounds without blocking the pressor responses to nonsympathomimetic compounds. The pressor effects of nonsympathomimetic compounds such as angiotonin and Pitressin are not blocked by Dibenamine.[18–20] Presumably, the site of action of these compounds is directly upon the contractile mechanism.

(2) *Effects of l-Epinephrine and l-Norepinephrine upon Arterial Blood Pressure.* Dibenamine

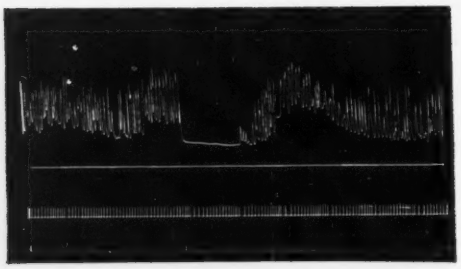

FIG. 4. The effect of the extract of tumor A upon the motility of a segment of jejunum in the form of a Thiry fistula. The writing points from above down indicate: record of intestinal motility by means of a mercury manometer, zero pressure, time in five second intervals, and time of intravenous injection of 0.2 cc. of tumor extract. The response is typical of that produced by sympathomimetic compounds.

produces a blockade at certain excitatory adrenergic neuroeffector junctions, but it does not block inhibitory adrenergic functions. Following the administration of Dibenamine, according to the doses and time relations indicated by Nickerson and Goodman,[21] epinephrine produces a typical depressor response. This is due, presumably, to the "unmasking" of the vasodilator action of epinephrine. Their earlier studies indicated that the pressor effects of norepinephrine are blocked by Dibenamine, but that little or no reversal occurs because of the weak vasodilator action of norepinephrine. A later report by Nickerson[22] indicated that the time required for Dibenamine "fixation" in the tissues was probably nearer 90 minutes than 30 minutes; and epinephrine given within a 90-minute period after Dibenamine reduced the effectiveness of the blockade, possibly by competing with Dibenamine for its site of action.

The assays of each tumor were begun 30 to 40 minutes after the completion of Dibenamine administration. Multiple injections of epinephrine were given both before and after Dibenamine. The dissimilar results obtained in the bioassay of the tumors, and unanticipated inconsistencies in the action of Dibenamine suggested that the pressor responses observed in tumor A after Dibenamine were, in reality, due to incomplete adrenergic blockade by Dibenamine. This led to an additional series of experiments in which the effects of l-epinephrine and l-norepinephrine upon the arterial blood pressure were compared after varying time and dose relations of Dibenamine.

The first group of experiments was done upon 4 dogs anesthetized with sodium pentobarbital. Two dogs were given 15 mg. per Kg. of Dibenamine and 2 were given 30 mg. per Kg. Equipressor doses of l-epinephrine and l-norepinephrine were injected alternately before Dibenamine and 30 to 40 minutes after the completion of Dibenamine administration. In the 2 dogs in which 15 mg. per Kg. of Dibenamine was used, l-norepinephrine produced a distinct pressor response in one dog with the second injection of l-norepinephrine after Dibenamine. Subsequent doses of l-norepinephrine ranging from 1 cc. of 1:1000 to 1 cc. of 1:50,000 concentration consistently produced pressor responses. In the second dog, a distinct pressor response occurred with the sixth injection of l-norepinephrine after Dibenamine. Of the 2 dogs in which 30 mg. per Kg. of Dibenamine was used, one animal failed to show pressor responses to 3 successive injections of l-norepinephrine 30 minutes after Dibenamine in doses as large as 10.0 cc. of 1:50,000 concentration. In the second dog, 2 cc. of 1:50,000 l-norepinephrine was given as the initial injection 30 minutes after Dibenamine, and produced a small but distinct pressor response. Further injections of l-norepinephrine resulted in pressor responses of the same magnitude.

In each of the four dogs, a wide range of doses of l-epinephrine produced depressor responses.

In two dogs, no injections were given prior to Dibenamine or less than two to three hours following the administration of 15 mg. per Kg. of Dibenamine. Injections of l-epinephrine and l-norepinephrine were then given alternately. Two hours after Dibenamine administration, the first and second injections of l-norepinephrine (1 cc. 1:50,000 and 1 cc. 1:1000 respectively) produced slight reductions of blood pressure. The third injection of l-norepinephrine (0.5 cc. 1:50,000) and subsequent injections each produced a pressor response. This is shown in figure 5. In the second dog, the first injection given after the three hour interval was 0.5 cc. 1:50,000 l-norepinephrine. A definite pressor response was obtained. In both dogs, l-epinephrine produced only depressor responses.

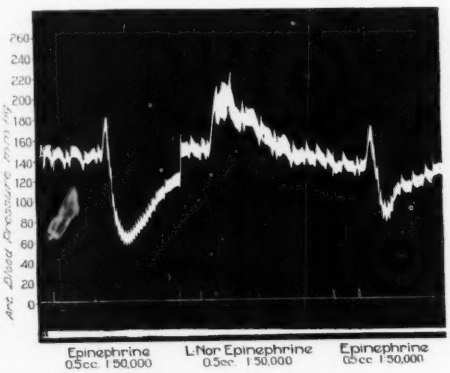

FIG. 5. Comparison of the effect upon arterial blood pressure of l-epinephrine and l-norepinephrine two hours following the injection of 15 mg. per Kg. of Dibenamine. No compounds were injected during the two hour interval.

(3) *Effects of Dibenamine upon Arterial Hypertension Produced by Constant Intravenous Infusions of l-Epinephrine and l-Norepinephrine.* A pheochromocytoma which produces a sustained hypertension presumably does so by the more or less constant liberation of epinephrine or an epinephrine-like substance into the circulation. If the injection of epinephrine during or soon after the administration of Dibenamine decreases the effectiveness of the adrenergic blockade, as has been suggested by Nickerson[22] and supported by the experiments described above, the explanation of the neutralization by Dibenamine of the major part of the hypertension associated with pheochromocytomas is not readily apparent. Acute experiments were done in an attempt to simulate the sustained hypertension associated with some pheochromocytomas, and to study the effect of Dibenamine upon such hypertension.

Constant intravenous infusions of either l-epinephrine (1:25,000) or l-norepinephrine were given to three dogs by means of a power-driven syringe. The rate of injection was adjusted until the desired level of hypertension was obtained. A dose of 15 mg. per Kg. of Dibenamine was then injected intravenously during an eight minute period. Two of the 3 dogs received l-norepinephrine infusions and the third dog received an infusion of l-epinephrine. In each instance the drug infusions began 10 to 20 minutes prior to the injection of Dibenamine, and were continued throughout the period of Dibenamine administration. One l-norepinephrine infusion was continued for 60 minutes after Dibenamine, and the remaining l-norepinephrine and l-epinephrine infusions were continued for 20 minutes after Dibenamine. Within five minutes after the beginning of the injection of Dibenamine, the arterial blood pressure declined steadily to the pre-hypertensive level, in the case of the l-norepinephrine infusions, and to below the pre-hypertensive level in the l-epinephrine infusion. If the infusions were momentarily discontinued 1 to 10 minutes after completion of Dibenamine injection, the arterial blood pressure returned to the pre-hypertensive level. When the l-norepinephrine infusions were started again at the same rate, the arterial blood pressure increased but only one-third as much as it did before Dibenamine. When the l-epinephrine infusion was started again, the arterial blood pressure fell below the pre-hypertensive level. Single injections of l-epinephrine (1 to 2 cc. 1:50,000) produced pressor responses 20 minutes after Dibenamine and slight reductions of arterial blood pressure 40 to 60 minutes after Dibenamine. Single injections of l-norepinephrine (2 cc. 1:50,000) produced consistent pressor responses when injected 20 to 60 minutes after Dibenamine.

Discussion

The results of these experiments indicate that, with the time and dose relations of Dibenamine which were used, the pressor response to l-norepinephrine is not always blocked, and its effects upon the arterial blood pressure after Dibenamine are unpredictable. The failure of Dibenamine to block the pressor activity of l-norepinephrine in dosages which are considerably greater than those necessary to block and to reverse the pressor response to all doses of l-epinephrine, indicates that Dibenamine cannot be used to differentiate pressor responses due to sympathomimetic and nonsympathomimetic compounds when norepinephrine is involved. Various other adrenergic blocking agents such as N-piperdino-methyl-benzodioxane (933 F), yohimbine, ergotamine, and ergotoxine are known to be less effective in blocking the pressor activity of l-norepinephrine than of epinephrine.[3, 12, 13, 23–25] In accordance with the observations of Nickerson,[22] epinephrine injected during the administration of Dibenamine, or soon after, decreases the effectiveness of the adrenergic blockade.

The findings in tumor A are compatible with the reports of the presence of norepinephrine in pheochromocytomas[7, 14, 15, 17, 26] to the extent that the actions of the pressor substance after Dibenamine resembled those of norepinephrine rather than epinephrine. The consistent depressor responses to extracts of tumor B after Dibenamine indicate that the major pressor principle in this tumor was epinephrine, but the presence of norepinephrine is not excluded since the assay method is not quantitatively accurate. The absence of a pressor response to extracts of tumor B after Dibenamine, in contrast to tumor A, is similar to the results of Beyer[17] who has recently bioassayed two pheochromocytomas by the same method. The pressor actions of the extracts of these tumors were abolished after incubation with amine oxidase. He calculated that the norepinephrine content of the two pheochromocytomas was approximately 50 per cent and 90 per cent.

Pheochromocytomas generally contain a higher percentage of norepinephrine than does normal adrenal medullary tissue. Goldenberg[7] reported three tumors in which the norepinephrine content ranged from 53 per cent to 90 per cent; Holton[14, 15] assayed three tumors which contained from 60 per cent to more than 90 per cent norepinephrine, and Calkins[26] reported a tumor containing approximately 83 per cent norepinephrine. The presence of norepinephrine in both normal and pathologic adrenal medullary tissue suggests that norepinephrine may be a precursor of epinephrine or that norepinephrine may be liberated as such directly into the circulation. Blaschko[27, 28] has proposed that norepinephrine is the precursor of epinephrine, and that the secondary amine, epinephrine, results from the methylation of the primary amine, norepinephrine. Bülbring and Burn[29] perfused suprarenal glands of dogs with heparinized blood and found that there was an increase in the secretion of epinephrine when norepinephrine was added to the perfused blood. Bülbring[30] demonstrated that incubated suspensions of dog and cat adrenal glands are capable of converting norepinephrine to epinephrine. She concluded from her studies that epinephrine is produced from norepinephrine through a transmethylation reaction in the adrenal medulla. The presence of greater amounts of norepinephrine in adrenal medullary tumors suggests the possibility of impairment in the transmethylation reaction.

The possibility of direct liberation of norepinephrine into the circulation has received the attention of several investigators. Following continuous stimulation of the splanchnic nerves in the chloralosed cat, West[31] observed that epinephrine liberation gradually decreases until at the end of one hour 70 per cent of the active material from the adrenal gland is norepinephrine. Bülbring and Burn[4] stimulated the splanchnic nerves of spinal cats from which the viscera had been removed and the renal circulation excluded. Under these conditions splanchnic stimulation liberated from the adrenal gland a mixture of epinephrine and norepinephrine in which the norepinephrine content varied from 20 to 80 per cent. There is little information concerning the possibility that norepinephrine is liberated into the circulation from adrenal medullary tumors although Vogt[32] has recently reported the detection of

circulating norepinephrine in a case of pheochromocytoma. We have been unable to determine by the response of the arterial blood pressure to Dibenamine either the nature or the amounts of pressor substance or substances which are liberated into circulation from pheochromocytomas. The arterial hypertension produced in dogs by the constant intravenous infusion of l-norepinephrine or l-epinephrine was abolished by the injection of 15 mg. per Kg. of Dibenamine. Such a result is difficult to explain in view of the frequent failure of Dibenamine to block the pressor effects of single injections of l-norepinephrine where the conditions for the development of adrenergic blockade are most favorable. The demonstration of the presence of l-norepinephrine in adrenal medullary tumors does not justify the assumption that this is the substance being liberated into the circulation. Attempts to correlate bioassay findings with the clinical features of pheochromocytomas must be deferred until more information is available concerning the nature of the active substance or substances which are liberated by these tumors.

The demonstration of norepinephrine in the adrenal medulla as well as in various adrenergic nerves strengthens the concept that this compound is an intermediary in the production of epinephrine. Two observations indicate that this is the case rather than that epinephrine is the precursor of norepinephrine. First, the epinephrine: norepinephrine ratio is higher in normal than in tumorous adrenal medullary tissue. Second, the more physiologic the conditions under which epinephrine is liberated from the adrenal medulla, the greater the proportion of epinephrine released.

The view may be restated[33] that norepinephrine is concerned with epinephrine metabolism in all of the tissues which produce epinephrine. It is likely that both excitatory and inhibitory adrenergic nerves and the adrenal medulla produce epinephrine by the same steps and that the last step in the series of reactions is the conversion of norepinephrine to epinephrine. It is possible that, from all sources, some norepinephrine enters the circulation and that from some sources under certain conditions the proportion of norepinephrine entering the circulation may be increased. It is probably an oversimplification to consider that excitatory adrenergic nerves liberate only norepinephrine and inhibitory adrenergic nerves liberate only epinephrine.

Summary and Conclusions

1. Two cases of pheochromocytoma are reported. The tumors were bioassayed by comparing the effects of the tumor extracts upon the arterial blood pressure of dogs before and after the administration of the adrenergic blocking agent, Dibenamine.

2. One tumor contained predominantly a substance resembling norepinephrine. The second tumor contained chiefly an epinephrine-like substance.

3. Dibenamine is similar to other adrenergic blocking agents in its inability to block uniformly the pressor action of norepinephrine.

4. The role of norepinephrine in epinephrine metabolism is discussed.

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Effect of Strophanthus on Coronary Blood Flow and Cardiac Oxygen Consumption of Normal and Failing Human Hearts

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The action of strophanthus preparations on the coronary blood flow and the oxidative metabolism of the normal and failing human heart has been studied by coronary sinus catheterization. It has been found that strophanthus preparations have no effect on the coronary flow or oxidative metabolism of either the normal or failing heart. This agrees with the concept that the oxidative metabolism (energy production) of the failing heart in vivo is not abnormal. The results indicate that this drug is responsible for causing more effective conversion of oxidative energy into work.

THE EFFECT of various digitalis preparations on the circulation of patients with and without cardiac failure has been studied by a large series of investigators.[1–9] Quantitative measurements of the effect of digitalis on cardiac oxygen consumption and efficiency of the human heart in vivo have not been published to date because of difficulties in the methods involved. Catheterization of the coronary sinus in man in conjunction with the nitrous oxide method has now made it possible to determine cardiac oxygen consumption and coronary blood flow in man,[10] and to study quantitatively the effect of digitalis on the energy metabolism of the normal and failing human heart in vivo. This report deals with the effect of strophanthus preparations on the coronary blood flow and cardiac oxygen consumption of patients with and without cardiac failure.

Methods

The coronary sinus was catheterized according to a method previously described.[11] Coronary blood flow was determined by means of the nitrous oxide method.[10] Cardiac output was measured with the direct Fick principle, the mixed venous samples being obtained from the right ventricle or the pulmonary artery by means of an intracardiac catheter.[12] Peripheral arterial pressures were optically recorded with strain gages or obtained with the sphygmomanometer.

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Coronary blood flows and cardiac oxygen consumption were obtained for 100 Gm. of cardiac tissue.[10] These values may be considered accurate. Because of difficulties in defining accurately that portion of cardiac muscle which has its venous drainage into the coronary sinus[13] and because of inaccuracies in calculating the heart weight from height and weight of the patient,[14] figures for mechanical efficiency and energy cost of the heart must be considered only approximations. However, since major variations in the distribution of coronary venous drainage are unlikely during the short period of the test, changes in cardiac efficiency and energy cost produced by the drug are quantitative and therefore significant. In the calculations of cardiac efficiency it was assumed that the tributaries of the coronary sinus drain primarily the left ventricular muscle.[13] Consequently, the work–energy cost relationship was calculated for the left ventricle only. Recent observations of Gregg indicated that better correlations between results derived from the nitrous oxide method and direct determinations of flow can be obtained if the combined weights of the left auricle and ventricle are used.[15] However, in evaluating the effect of strophanthus preparations, only the relative changes from the control values are of importance.

In general, the procedure outlined in a previous report was followed.[10] After the first measurement of cardiac output, coronary flow and cardiac oxygen consumption, strophanthus K (0.65 mg. Burroughs Wellcome Co.) or strophosid (0.5 mg. Sandoz Chemical Works) were slowly injected intra-arterially through a manifold. After a 10 minute interval, the nitrous oxide mixture was again administered over a period of 12 minutes. Following this, coronary blood flow, cardiac oxygen consumption and cardiac outputs were again determined.

Cardiac work was expressed in kilogram meters per minute. It was calculated from the formula[10]:

TABLE 1.—*Effect of Digitalis on Coronary Blood Flow in Normal Subjects*

No.	Subj.	Sex	Age	Total Oxygen cons.	Systemic A-V O_2 diff.	C. O.	C. O.	Aortic mean pressure	L. V. work	Cor. Flow	Coronary A-V O_2 diff.	L. V. O_2 cons.	L. V. Weight	Energy cost of L.V.	Efficiency
				cc.	*Vols. %*	*L/Min.*	*L/Min./M²*	*mm. Hg.*	*Kg. M.*	*cc./100 Gm./min.*	*Vols. %*	*cc./100 gm./min.*	*Gm.*	*Kg. M.*	%
1	W. J.	M	35												
	Before			268	2.05	13.50	6.70	122	22.4	85	12.3	10.4	224	48.4	46
	After			269	4.90	5.54	2.77	120	9.0	76.4	13.3	10.2	224	47.0	19.1
2	A. R.	M	54												
	Before			230	2.37	9.70	4.95	111	14.6	63.2	10.8	6.9	208	29.6	49.0
	After			237	4.79	4.95	2.52	111	7.5	68.2	10.6	7.25	208	30.8	24.4
3	J. Z.	M	44												
	Before			224				118		98.6	9.77	9.60	177	35.0	
	After			244	5.24	4.68	2.70	124	7.84	117.7	11.25	13.2	177	48.1	10.3
4	J. B.	M	74												
	Before			189	2.6	7.25	4.26	97	9.5	76.6	12.3	9.3	170	32.8	28.2
	After			269	5.1	5.25	3.10	110	7.9	70.4	12.4	8.7	170	30.2	26.0
5	A. C.	M	54												
	Before			204	3.2	6.40 (dye)	4.00	87	8.72	85.0	9.74	8.28	151	25.7	34.0
	After			160		3.58	2.24	87	4.23	72.0	10.8	7.78	151	24.0	17.5
6	B. B.	F	32												
	Before			236	4.56	5.18	2.85	160	11.3	85.5	12.85	11.0	184	41.86	27.0
	After			216	6.10	3.50	1.92	135	6.52	96.6	13.08	12.6	184	47.9	13.6
7	Before	F	60	340	3.55	9.56	4.80	183	23.8	92.5	12.8	11.8	206	50.3	47.3
	After			207	7.01	2.9	1.48	183	7.34	81.4	13.5	11.0	206	46.7	15.7

TABLE 2.—*Effect of Digitalis on Coronary Blood Flow in Patients with Cardiac Failure*

No.	Subj.	Sex	Age	Total Oxygen conc.	Systemic A-VO_2 diff.	C. O.	C. O.	Aortic mean pressure	L. V. work	Cor. Flow	Coronary A-V O_2 Diff.	L. V. O_2 conc.	L. V. Weight	Energy cost of L. V.	Efficiency
				cc.	*Vols. %*	*L./min.*	*L/min./M²*	*mm. Hg*	*Kg. M.*	*cc./100 Gm./min.*	*Vols. %*	*cc./100 Gm./min.*	*Gm.*	*Kg. M.*	%
8	E. R.	F	52												
	Before			150	4.15	3.62	1.95	71	3.47	50.2	10.6	5.3	167	18.4	19.0
	After			193	5.24	3.70	1.96	84	4.24	53.6	10.6	5.7	167	19.5	21.8
9	J. H.	M		216	5.08	4.25	2.76	84	4.85	51.2	15.1	7.75	148	23.4	17.0
	Before														
	After			297	5.6	5.40	3.48	84	6.20	61.6	15.0	9.30	148	28.4	22.0
10	J. B.	M		211	5.2	4.10	2.14	92	5.20	111.0	14.5	16.1	196	64.8	8.0
	Before														
	After			280	3.25	8.60	4.50	95	11.1	127.0	14.1	18.0	196	73.0	15.2
11	A. McM.	M	45												
	Before			163	6.1	2.68	1.58	100	3.67	71.4	14.1	10.0	138	28.4	12.9
	After			229	4.8	4.78	2.80	100	6.50	79.2	15.0	11.9	138	33.7	19.3
12	F. R.	M	65												
	Before			200	5.1	4.3	2.5	101	6.2	117.0	11.4	13.3	145	39.7	15.6
	After			236	4.7	5.0	3.0	103	7.0	115.0	12.1	14.0	145	41.8	16.8

Work (Kg. meters/min.) = cardiac output (cc./min.) × mean aortic pressure (mm. Hg) × 13.6

To express the oxygen consumption of the left ventricle in the same units as left ventricular work the oxygen consumption was multiplied by the work equivalent of oxygen at a respiratory quotient of 0.82 (cc. oxygen = 2.059 Kg. meters).[10]

The following equation was used for the calculation of left ventricular efficiency[10]:

$$\textit{Mechanical efficiency of left ventricle (percentage)} = \frac{\textit{work of total left ventricle (Kg. meters/min.)}}{\textit{oxygen consumption of total left ventricle (Kg. meters/min.)}}$$

Coronary vascular resistance was calculated according to the equation:

$$\text{Coronary vascular resistance} = \frac{\text{mean aortic pressure (mm.Hg)}}{\text{coronary blood flow cc./100 Gm./min.}}$$

Consequently, the units for this resistance are expressed in mm.Hg/cc./100 Gm./min. The resistance calculated in this manner refers to that portion of the coronary vascular bed only which drains into the coronary sinus.

Results

The results obtained in normal individuals are illustrated in table 1. It may be seen that the cardiac output fell in every instance. This is in agreement with the findings of Cohn and Stewart[2] and McMichael and Sharpey-Schafer.[4] The arterial pressure remained constant. As a result of the fall in cardiac output, the left ventricular work decreased.

The coronary blood flow per 100 grams and the coronary arteriovenous oxygen difference also showed no significant change following the injection of the glycoside. Therefore, the cardiac oxygen consumption remained constant. Because of the fall in the work of the heart, the left ventricular efficiency decreased.

In failure due to arteriosclerotic heart disease or to mitral stenosis and insufficiency the initial cardiac output was low (table 2). The coronary arteriovenous oxygen difference and the left ventricular coronary blood flow were within normal limits. These results are in agreement with those previously published from this laboratory.[10] Table 2 illustrates that following the injection of strophanthus preparations, the cardiac output rose. Similar findings were obtained by Ahmed and associates,[16] Stead[6] and Bloomfield and co-workers.[5] The coronary blood flow and the coronary arteriovenous oxygen difference remained at the previous level. Therefore, the left ventricular efficiency rose following the injection of strophanthus preparations.

Discussion

The results published in a previous report show that the output of the heart in failure is reduced, while the oxygen consumption is normal. Similar results were obtained in this series in patients with failure. This indicates that while there is no defect in the utilization of the oxidative energy of the failing human heart in vivo, the heart is defective in converting oxidative energy into effective work. This is in agreement with the finding of Goodale and associates[20] that the aerobic oxidation pattern of the failing heart in vivo is normal. In line with this is the observation that strophanthus has no effect on the oxygen consumption of the failing heart but aids in a more effective conversion of oxidative energy into effective work. Thus, strophanthus increases the efficiency of the failing heart only by increasing the output. These findings contrast with those

Table 3.—*Effect of Strophanthus on Coronary Resistance*

Subj.	Mean Aortic Pressure		Coronary Flow/100 Gm.		Coronary Resistance	
	Before	After	Before	After	Before	After
					mm.Hg./cc./100 Gm./min.	
Normals						
W. J.	122	120	85.0	76.4	1.43	1.58
A. R.	111	111	63.2	68.2	1.76	1.63
J. Z.	118	124	98.6	117.7	1.20	1.06
J. B.	97	110	76.6	70.4	1.26	1.56
A. C.	87	87	85.0	72.0	1.02	1.14
B. B.	160	135	85	96.0	1.88	1.41
F. W.	183	153	92.0	81.0	1.99	1.89
Failure						
E. R.	71	84	50.2	53.6	1.41	1.56
J. B.	92	95	111.0	127.0	.82	.75
J. H.	84	84	51.2	61.6	1.64	1.36
A. McM.	100	100	71.4	79.2	1.40	1.26
F. R.	101	103	117	115	.86	.90

obtained by Starling and Visscher,[17] by Gremels[18] and by Moe and Visscher.[19] In all patients in cardiac failure in this series there was radiologic evidence of cardiac enlargement. The finding of cardiac enlargement existing in conjunction with normal cardiac oxygen consumption raises further doubt concerning the validity of Starling and Visscher's postulate that the total energy set free by the heart beat is solely a function of the diastolic volume.[17]

In the normal, strophanthus causes a decrease in the work of the heart, by reducing its output. The finding is in agreement with that of Stead[6] and McMichael.[4] As the energy cost remains unchanged, the efficiency decreases.

The effect of strophanthus on the resistance of the coronary vascular bed is illustrated

in table 3. It may be seen that changes in coronary vascular resistance following strophanthus are small. This indicates that the drug has no direct action on coronary blood vessels.

Summary

The effect of strophanthus preparations on coronary blood flow, cardiac oxygen consumption and efficiency has been measured in a series of patients with and without cardiac decompensation.

Strophanthus lowers the efficiency of the normal heart by reducing the cardiac output. The oxygen consumption of the heart is not affected. The oxygen consumption of the failing heart per 100 grams of muscle is normal. Strophanthus increases the efficiency of these hearts by elevating the cardiac output. Again the cardiac oxygen consumption remains unchanged.

Strophanthus has no significant effect on coronary vascular resistance, indicating that the drug has no direct action on coronary vessels.

The findings illustrate that there is probably no defect in the utilization of oxidative energy of the failing human heart in vivo, but the failing heart is defective in converting oxidative energy into effective work. Strophanthus aids in this conversion.

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Age, Serum Cholesterol and Coronary Artery Disease

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The question of an age-associated rise in serum cholesterol has been undecided. This communication presents evidence in favor of a rise in serum cholesterol with increasing age between the third and the fifth decades. In a control group of 146 individuals and a coronary disease group of 97 individuals, there was a positive correlation between age and serum cholesterol. In the coronary disease group, there was a rise in serum cholesterol superimposed upon an initially higher level of serum cholesterol. The concept of "cholesterol age" is presented on the basis that a patient with coronary heart disease at 25 has a serum cholesterol similar to a "normal" male at the age of 45. The role of serum phospholipids is considered in the age-associated rise in serum cholesterol.

SEVERAL STUDIES have concluded that there is probably a rise in the serum cholesterol level after puberty in the male[1, 2] while other reports have claimed no such relationship.[3, 4] Before puberty, however, the serum cholesterol level seems to be lower than in adult life,[5] and the evidence appears to support Sperry[6] who asserts that the cholesterol level is lowest during the neonatal period in (full term) infants and approximates adult levels in late prepuberty or early puberty.[6, 7] Page and his co-workers have concluded that no comparable rise exists postpubertally,[8, 9] although our calculation from their data did not entirely confirm this conclusion.

Sampling errors may account for some of the discrepancies, negative results and differences in opinion; several studies[4, 8] were conducted on groups too small to yield statistically significant results.[10] Also, individuals hospitalized for disorders presumed not to be related to cholesterol metabolism were included with the so-called "normals"[4] though no evidence has yet been offered that systematic errors do not appear in such procedures. Furthermore, the influences of race, diet, occupation and socio-economic status, though discussed in theory,[11–13] have in general not been considered in previous studies.

There is, at present, no unanimity on the possible relationship between serum cholesterol and age. It is not definitely known whether the cholesterol level is constant with advancing years or whether there are continuous changes with age and, if the latter is true, when the greatest changes occur. The increase in severity and frequency of arteriosclerosis with age and the possible relationships of arteriosclerosis and cholesterol make such a study of age changes of serum cholesterol worthwhile. Accordingly, this study was undertaken to determine the influence of age on serum cholesterol in both the normal individual and the patient with coronary artery disease.

METHOD AND MATERIALS

The blood for cholesterol determination was obtained in the manner described in a previous paper in this series. The Bloor technic was employed for these determinations.[14] Two groups are considered in this study: a coronary disease group and a healthy control group. The healthy control group consisted of 146 men who were working in a large industrial plant in Cambridge, Massachusetts. They were considered healthy by ordinary clinical standards and in addition showed no pathologic abnormalities in the electrocardiograms. Furthermore, they were rejected if they showed frequent absenteeism from work. In contrast, 97 males who had experienced myocardial infarction prior to the age of 40 comprised the coronary series. Two blood samples from the coronary disease group are not included because the patients were over 50 years of age at the time of examination. Both groups were comparable in age, occupation and race (predominantly northwest European). Each member of the coronary disease group was referred for study by private physicians, clinics, or the Veterans' Administration. Eighty-two per cent of the coronary disease group came from New England and the Atlantic states, and were similar to the control

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group in diet and general mode of life. The detailed analysis of the national and racial origins of the two groups is considered elsewhere.[15] Suffice it to say that the two groups were comparable with two exceptions; the normal group had 23 per cent Irish as compared to 1 per cent in the coronary group, and the latter group had 26 per cent Jews as compared to 1 per cent in the control group. The occupations likewise are examined elsewhere in detail,[15] and may be considered entirely comparable on the professional, semi-professional and craftsman levels with a negligible difference in the manual labor category.

Results

In the first paper of this series[16] it was reported that the average serum cholesterol in the coronary disease group was 286.5 mg. per cent with a standard error of 7.14, and the comparable mean value of the normal group was 225.3 mg. per cent with a standard error of 3.59, the critical ratio of the difference being

Table 1.—*Serum Cholesterol Values of Normal Individuals by Decades*

Decades	Number	Range	Mean ± Standard Error
20–29	20	149–297	195 ± 9.2
30–39	74	148–332	224 ± 4.8
40–49	46	175–331	236 ± 6.0
50–59	6	214–284	254 ± 13.5
Total	146	148–332	225 ± 3.6

7.91. This means that the difference in serum cholesterol is statistically highly significant.*

No attempt was made in the first paper to associate or correlate a possible serum cholesterol change with increasing age in either group. When such a calculation in the normal group was made, the level of serum cholesterol was shown to rise with age as is evident from table 1. Thus, there is a constant progression from decade to decade, though the rise is not always statistically significant. The greatest rise is from the third to the fourth decade (ages 20–29 to 30–39). In order to express the strength of this association between age and cholesterol over the entire age range, a suitable measure is necessary.

* A significant difference in statistical usage is one that would not be expected on a chance basis and is not to be confused with the popular meaning, i.e., "important." (Small sample formula, Snedecor, 1946, pp. 81–82.[17])

The best single measure of concomitant variation between two variables in the coefficient of correlation, usually designated as r. Values of r vary from 0 (complete independence) to +1.0 (perfect positive correlation) and −1.0 (perfect negative correlation). The coefficient of correlation for the whole healthy control series is +0.30 with a standard error of ±0.08. While not high in terms of predictability, this r is highly significant statistically ($p = < 0.01$) and indicates a positive association between age and serum cholesterol.

Computations on the coronary disease group likewise show a steady rise with age as shown in table 2.

The serum cholesterol in the coronary disease group is higher at any corresponding decade

Table 2.—*Serum Cholesterol Values of Male Coronary Disease Patients by Decades*

Decades	Number	Range	Mean ± Standard Error
20–29	7*	194–400	245 ± 27
30–39	53	167–490	286 ± 9
40–49	35	208–490	301 ± 11
Totals	95	167–490	288.0 ± 6.7

* Small sample formula employed.

level than it is in the healthy control group. In addition to this initially high serum cholesterol is the normal "physiologic" rise of serum cholesterol with age, particularly between the third and fifth decades. The rise is apparent between the third and fourth decades, but does not quite reach significance ($p = .06$, and for significance $p = .05$). The correlation coefficient between cholesterol and age in the coronary group is +.16 ± .10, not significantly different from zero ($p = .10$). This correlation is probably not significant since it does not exceed twice its probable error. However, it cannot be said that the association between age and cholesterol in the coronary group (+.16) is significantly less than in the normal group, for the difference between the two (.14) is not a significant one. Therefore, the apparently lower r in this case may have arisen as a sampling variation.

When the differences between the two groups are subjected to tests of significance, decade

by decade as in table 3, both means and standard deviations (a measure of variability or dispersion around the mean) are markedly higher in coronary patients than among normal subjects.

Since there is a rise in cholesterol with age in both groups (see fig. 1) and since there is a significant correlation in one and a possibly significant correlation in the other, it seems

TABLE 3.—*Comparison of Serum Cholesterol Means and Standard Deviations at Various Decades between Normal Group (N) and Coronary Disease Group (C)*

Decade	Number		Mean Cholesterol			Standard Deviation		
	C	N	C	N	Signf-icance	C	N	Signif-icance
20–29	7	20	245	195	*	71	41	*
30–39	53	74	285	224	†	62	42	*
40–49	35	46	301	236	†	66	41	*
Totals...	95	140‡	288	225	†	65	43	*

* Significant.
† Highly significant
‡ Six individuals between 50–59 are not considered in this paper.

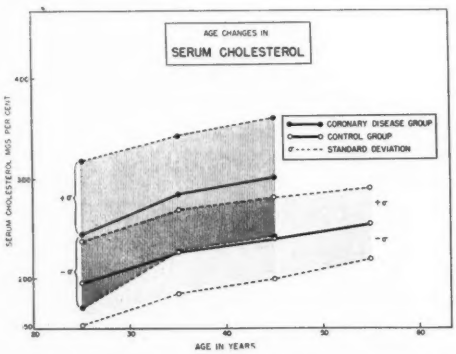

FIG. 1. Changes in serum cholesterol with age in the coronary disease group and the control group.

likely that age and cholesterol are co-variant. Page and his associates, on the other hand, did not find such a relationship. Their data were differently handled; no product-moment r was calculated, and very few individuals were included in each decade group. Therefore, it was decided to recalculate their data in order to determine whether when similarly handled the apparent discrepancy would be eliminated. The results are summarized in table 4.

As shown, there is no evidence of a dramatic rise in cholesterol with age, but there is a suggestion that lower ages were associated with lower cholesterol values and vice versa. Therefore, a coefficient of correlation was calculated in order to see whether serum cholesterol and age were co-variant in the study by Page and associates. Employing their data for individuals between 21 and 79 (eliminating the 12 eldest individuals in order to straighten the regression curve), a correlation of $+.26 \pm .13$ was ob-

TABLE 4.—*Serum Cholesterol in Healthy Adult Males at Various Ages*

Age	N	Mean ± Standard Error
20–39	9	225 ± 23
40–49	10	237 ± 12
50–59	13	236* ± 18
60–69	10	236 ± 18
70–79	10	268 ± 15
80–91	12	214 ± 13
Total.....	64	

Based on data of Page and co-workers.[5]
* If one reading of 428 is retained, N = 14; M = 250 ± 22, S.D. = 82.

tained. This is statistically significant on the 1 in 20 (i.e., .05) level, and the association is said to be moderately significant.

Since correlation is not synonymous with causation, a causal relationship cannot be postulated between serum cholesterol and age in the present study and in the data of Page and co-workers. There are many explanations for an association between two variables, such as: (a) an actual causal relationship between the two when all other influential factors are ruled out; (b) a primary correlation of each trait not with the other, but with another or several other intercorrelated traits.

In view of the seeming importance of these relationships, the properties of serum phospholipids and their ratios and age changes were investigated more intensively. Since simple correlations alone did not correct all interfering variables, the technic of partial correlations was employed. Thus, if both A and B affect C, it is possible to see the effect of B on C corrected for the presence of A.

It is apparent from table 5 that the phospholipids are highly correlated with cholesterol and show even higher correlations with age than does cholesterol in both the healthy and the coronary disease groups. Since all three variables are intercorrelated, it was decided to employ the technic of partial correlation which would theoretically determine the primary correlations of any pair of variables with

TABLE 5.—*Coefficients of Correlation (r): with Serum Cholesterol (1), Serum Phospholipids (2),* and Age (3) in Adult Men in Health and in Coronary Artery Disease*

	Normals		Coronary Artery Disease	
	N	R	N	R
r_{12}†	146	+.66 ± .05	61‡	+.51 ± .09
r_{13}	146	+.30 ± .08	95	+.16 ± .10
r_{23}	146	+.42 ± .07	61	+.20 ± .12

* Phospholipids are expressed as lecithin which is considered to be 25 times the blood lipid phosphorus level.

† r_{12} means that coefficient of correlation is between serum cholesterol and serum phospholipids.

‡ Only 61 phospholipids out of 62 were taken simultaneously with serum cholesterol.

TABLE 6.—*Partial Correlations among Cholesterol (1), Phospholipids (2), and Age (3), in the Serum of Adult Men in Health and with Coronary Artery Disease*

	Healthy Controls		Coronary Disease Group	
	N	Partial Correlation	N	Partial Correlation
$r_{12.3}$*	146	+.62 ± .05	61	+.50 ± .10
$r_{13.2}$	146	+.05 ± .08	95	+.07 ± .10
$r_{23.1}$	146	+.32 ± .07	61	+.14 ± .13

* $r_{12.3}$ means that the partial correlation is between cholesterol and phospholipids with age kept constant (See Lindquist, p. 249).[18]

the third held constant. The significance of this correlation will be discussed later. These correlations are tabulated in table 6.

It is apparent from table 6 that (a) in both health and coronary artery disease the cholesterol-phospholipid correlation is high, independently of age; (b) the correlation of cholesterol and age disappears when the influence of phospholipids is removed; (c) the phospholipids tend to remain correlated with age in the healthy group, but may not keep pace with age in coronary artery disease.

The difference between the two partial coefficients of correlation (+.32 ± .07 in health and 0.14 ± .13 in coronary artery disease) does not reach significance (p = 0.20), probably because of the small size of the coronary sample, but there is other evidence that the phospholipids play an altered role in coronary artery disease.

DISCUSSION

In the two groups considered here, one a group of healthy men and the other a group of men who had experienced myocardial infarction prior to the age of 40, a significant positive correlation is found between age and total serum cholesterol. This rise is not only reflected in the product-moment correlation r but also in comparing the mean values of the various decade groups and, in data collected by this project, by noting the statistical significance of the difference between decade groups.

The general rise between the third and fifth decade appears to be most marked in these data between the third and fourth decade. While the corrected yearly increase would be small (approximately 2.0 mg. per cent of total cholesterol per year), the decade increase would not be important; but a rise over two or three decades would be important in terms of a normal distribution of serum cholesterol values in man. At the age of 50 only 19.23 per cent of males have the cholesterol values typical of youth; conversely, 14.3 per cent of young individuals have serum cholesterol levels typical of the older male.

Since it was anticipated that individuals showing coronary artery disease might, as a group, show elevated serum cholesterol levels, it was thought possible that the normal or physiologic age changes might be masked in this group. Despite their hypercholesterolemia, however, the coronary disease group still show the physiologic age-rise in cholesterol. The two factors may thus be additive rather than potentiative in so far as coronary artery disease is concerned.

Based on the findings of Boas[12] and these

data, the level of serum cholesterol may be made up of three independent variables: (a) idiosyncratic, probably genetically determined hypercholesterolemia; (b) individual's basic physique-corrected cholesterol; (c) normal age influenced rise in cholesterol.

Under these circumstances the aboslute cholesterol level of an individual can be considered as meaning little to the clinician unless these other factors are known. By extending this reasoning the clinician might employ the concept of "cholesterol age"; since low cholesterol levels are more typical of youth and higher cholesterol levels are more typical of old age, one may simply consider an individual with a low serum cholesterol level as one with a "young cholesterol age." An individual who has an elevated cholesterol may be considered to have an "older cholesterol age." However, to derive the most benefit from such a concept, the magnitude of the difference between the chronologic age and the cholesterol age should be considered. This will become more apparent when one recalls that a patient 25 years of age with coronary artery disease has a serum cholesterol level the same as, or higher than a healthy individual 45 years of age; the values for both individuals average 245 mg. per cent and 236 mg. per cent, respectively.

There is some evidence that beyond the sixth decade of life no further elevation of cholesterol occurs, and that there may even be a drop in cholesterol level after this time (see table 4). While this has been interpreted by some as evidence of "debility" in age, it is more likely that it is a statistical phenomenon due to the differential mortality of low-cholesterol and high-cholesterol individuals. Thus, if elevated cholesterol is associated with decreased longevity, then the longer-lived individuals in an older group would simply be the low-cholesterol surviving population. It is possible, therefore, that such data, though scanty, may point to basic factors in human survival.[19,20]

The tabular material provided in the preceding section illustrates the need for larger samples in each decade or age group than have been customarily used in previous studies. Thus, the small size of decade samples in the study by Page and associates masked a slight but real correlation between age and cholesterol.

In this study, only a cross section of a population between the third and sixth decades was studied. Obviously, the best method of study to learn the age influence of cholesterol would be the longitudinal study to follow individuals from infancy to old age.

In this discussion, the relationship between cholesterol and age is considered with some suggestions that the cholesterol does not increase infinitely, but that a more stable period appears at some time during middle age. If this is so, why should atherosclerotic disorders increase after this period? The answer appears to lie (on the basis of partial correlation and previous data) not in the absolute cholesterol levels but in the relationship between cholesterol and the other serum lipids. As we have reported in the first paper in this series, there is an important difference in various lipid levels in coronary artery disease and in health. Thus, individuals who have hypercholesterolemia, but who are healthy and well, differ in cholesterol: phospholipids ratios from individuals of comparable cholesterol level who have experienced coronary artery disease. Moreover, individuals who have experienced coronary artery disease but who have low cholesterol levels still differ from normal individuals with identical cholesterol levels: this difference expresses itself in various lipid ratios, especially in the cholesterol: phospholipids ratio.

It is apparent from table 6 that (1) in both health and coronary artery disease the cholesterol-phospholipids correlation is high, independently of age; (2) the correlation of cholesterol and age disappears when the influence of phospholipids is removed; and (3) the phospholipids in the healthy individuals tend to remain correlated with age, but may not keep pace with age in coronary artery disease. The difference between the two partial r's, $+.32$ in health and $+.14$ in disease, fails to reach statistical significance ($p = .20$) because of the small size of the coronary sample. One interpretation of these findings, at this juncture, is to stress again the importance of serum phospholipids in the normal aging process and, particularly, in coronary artery disease.

Summary and Conclusions

1. The serum cholesterols were determined in 146 healthy, working males and 95 males who had experienced myocardial infarction prior to the age of 40. The control group and the coronary disease group approximated each other in age, ethnic and racial origin, and occupation.

2. A steady and significant rise in the level of serum cholesterol occurs with increasing years between the third and sixth decades in the healthy control (normal) group ($r = +.30 \pm .08$).

3. A steady, but less marked rise in the level of serum cholesterol occurs with increasing years in the coronary disease group between the third and sixth decades. In this group, the normal physiologic rise is superimposed upon the initial pathologic rise ($r = +.16 \pm .10$).

4. At every age level between the third and sixth decase the coronary disease group has markedly higher and more variable serum cholesterol levels than the healthy group.

5. Serum phospholipids are highly correlated with serum cholesterol in both health ($r = +.66 \pm .05$) and disease ($r = +.51 \pm .09$).

6. Serum phospholipid levels rise at least as much as serum cholesterol levels with age in health ($r = +.42 \pm .07$) and probably to a lesser extent in disease ($r = +.20 \pm .12$).

Partial correlations show that serum cholesterol and serum phospholipids remain highly correlated independent of age; the association between age and cholesterol disappears when the effect of phospholipids is removed; and, with the effect of cholesterol removed, phospholipids keep pace with age in health but apparently fail to do so in coronary artery disease.

7. It is hypothesized that the levels of serum cholesterol and serum phospholipids are less important in coronary artery disease than is the ratio of cholesterol and phospholipids.

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The Effect of Desiccated Thyroid on Plasma and Tissue Lipids and Atherogenesis in the Stilbestrol-Treated Chick

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Repeated implantations of diethylstilbestrol pellets cause a sustained hyperlipemia in the chick, and atherosclerosis eventually supervenes. Desiccated thyroid significantly reduces the incidence and degree of the stilbestrol-induced atherosclerosis in the chick, although it is without sustained effect upon the plasma and tissue lipids.

THE EXHIBITION of estrogenic substances elicits an increase in the concentration of plasma lipids in the chick.[1–3] If the hyperlipemia is maintained for several months by repeatedly implanting pellets of diethylstilbestrol, atherosclerosis is induced.[4, 5] We have previously shown that desiccated thyroid lowers hyperlipemia and hypercholesterolemia in cholesterol-fed chicks. Concomitantly, this hormone reduces the incidence, extent and severity of cholesterol-induced atherosclerosis.[6, 7] These findings led us to study the effect of desiccated thyroid in stilbestrol-implanted chicks, in order to determine if hormone interrelations known to affect endogenous lipid metabolism manifest themselves in an altered incidence and degree of atherosclerotic lesions.

Methods

One day old Hy-Line cockerels were obtained from a certified hatchery and raised in a battery brooder. They were fed a commercial chick starter mash (plain mash) of known composition.[8] At 8 weeks of age, 30 birds were divided into 3 groups of 10 chicks each: Group 1 birds subsisted on plain mash and received subcutaneous implantations of diethylstilbestrol pellets (25 mg.)* at 3 week intervals. Group 2 chicks were implanted with stilbestrol and fed thyroid mash (99.5% plain mash + 0.5% desiccated thyroid.†) The control group (Group 3) received only plain mash.‡

All birds were weighed weekly and a record of feed intake was maintained. They were bled periodically from the alar vein. Pooled aliquots of plasma were analyzed for the various lipid fractions by the methods of Schoenheimer and Sperry[9] and Man et al.[10, 11] Plasmas from 3 or 4 birds of a group were pooled, and 2 sets of pooled plasmas were analyzed each time. Autopsies were done on all birds which succumbed during the course of the experiment. After twenty-five to twenty-seven weeks on the diet, surviving chicks were sacrificed by decapitation and exsanguination. All the viscera were examined and the gross findings recorded. The hearts and great vessels (aorta, brachiocephalic and iliac arteries) were carefully inspected for evidence of gross atheromatous plaques. Lesions, if any, were described and recorded graphically on special forms; the aortas were graded 0 to 4 for atheroma, according to criteria previously described.[12] During grading, specimens from different groups were indiscriminately mixed and examined consecutively as unknowns. Blocks of tissue were taken for microscopic examination and fixed in 10% aqueous formalin. Frozen sections were stained with hematoxylin-eosin. At the end of the experiment, pooled aliquots of liver and aorta were analyzed for lipids (total and free cholesterol, lipid phosphorus, total fatty acid) according to procedures previously described.[8–11] Livers and aortas of 2 or 3 chicks of a

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† We are indebted to Drs. J. R. Mote and L. P. Anderson of the Armour Laboratories, Chicago, Illinois, for donating the desiccated thyroid for this study.

‡ Concomitantly we studied the effects of thyroid on lipid metabolism and atherogenesis in chicks fed plain mash. The findings, which are being prepared for publication, are not significant with respect to control data for the present study.

group were pooled, and 2 analyses per group were conducted.

Results

Growth and development. No significant differences in feed intake were noted among the three groups. The stilbestrol–plain mash chicks (Group 1) became heavier than any of the other groups, apparently because of hormone-induced deposition of fat.[5, 13, 14] The stilbestrol-thyroid mash birds (Group 2) exhibited the slowest rate of weight gain.

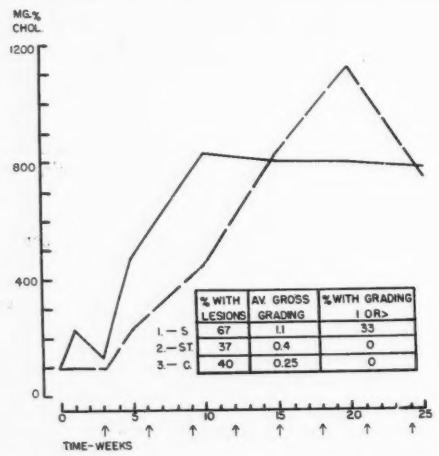

FIG. 1. Effect of thyroid on plasma cholesterol levels (graph) and atherosclerosis (table, lower right) in stilbestrol-implanted chicks. The arrows (↑) indicate subcutaneous implantations of 25 mg. pellets of diethylstilbestrol. Throughout the experiment, control (Group 3) chicks, fed plain mash and given no hormone, maintained a steady plasma cholesterol level of approximately 100 mg.% (see value at 0 weeks). Discussed in text. (Solid line = stilbestrol; broken line = stilbestrol-thyroid.)

Plasma lipids. The mean data on plasma lipids are presented in figures 1 and 2 and table 1. In accord with previous reports,[4, 5] stilbestrol implantation induced a hyperlipemia involving all plasma lipid elements. Lipid phosphorus exhibited the greatest increment; the increase in plasma cholesterol was less marked. Consequently the ratio total cholesterol/lipid phosphorus decreased (fig. 2). Stilbestrol implantation also consistently induced an increase in the plasma ratio free cholesterol/ total cholesterol (table 1).

The exhibition of desiccated thyroid to stilbestrol-implanted chicks led to a decrease in hypercholesterolemia and hyperphospholipemia during the first weeks of the experiment (figs. 1 and 2, table 1). Thus, at one week, the stilbestrol–plain mash birds had a mean plasma total cholesterol and lipid phosphorus of 220 and 31.3 mg. per cent respectively (ranges: 215–237 and 29.2–33.3 mg. per cent). The stilbestrol–thyroid mash birds (Group 2, table 1) had significantly lower mean values, i.e. 101 and 13.3 mg. per cent respectively (ranges: 93–109 and 12.2–14.3 mg. per cent respectively). These plasma cholesterol levels are well within the normal range. The lipid phosphorus values are elevated. Hence the ratio total cholesterol/lipid P was decreased. The

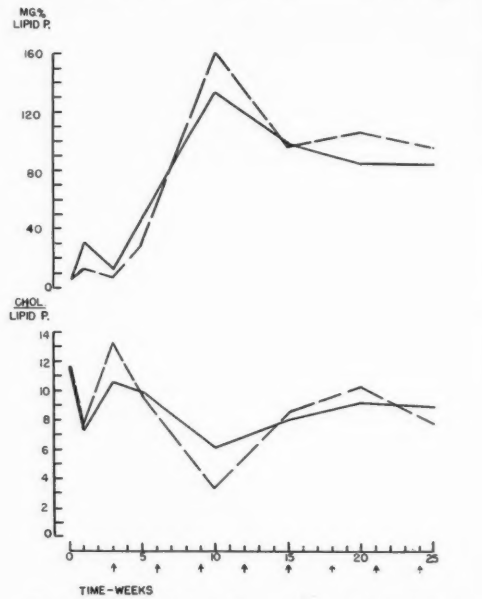

FIG. 2. Effect of thyroid on plasma phospholipids (upper graph) and ratio cholesterol/lipid phosphorus (lower graph) in stilbestrol-implanted chicks. Phospholipid levels are expressed in terms of lipid phosphorus. The arrows (↑) indicate subcutaneous implantations of 25 mg. pellets of diethylstilbestrol. Throughout the experiment the control (Group 3) chicks, fed plain mash and given no hormone, maintained a steady level of plasma lipid phosphorus (approximately 7.0 mg.%) and of cholesterol/lipid phosphorus (approximately 11.5) (see values at 0 weeks). Discussed in text. (Solid line = stilbestrol; broken line = stilbestrol-thyroid.)

desiccated thyroid diet also tended to keep the plasma ratio free cholesterol/total cholesterol at normal levels (table 1). At five weeks, the plasma lipid pattern was similar to that observed at 1 week, except that thyroid exhibition no longer completely prevented moderate hypercholesterolemia and elevation of the ratio free cholesterol/total cholesterol. By ten weeks the two stilbestrol-implanted groups had similar plasma lipid phosphorus levels (fig. 2), although hypercholesterolemia remained less severe in the thyroid-fed birds. At fifteen weeks and thereafter, the pattern of hypercholesterolemia and hyperphospholipemia was essentially similar in the 2 groups of stilbestrol-implanted chicks (figs. 1 and 2, table 1).

After twenty-seven weeks of treatment, both experimental groups had a moderate hepatic and aortic cholesterosis and lipidosis (table 1). These tissue lipid levels in the two treated groups represent significant elevations. Consistent with plasma findings at this time, no significant differences between Group 1 and 2 in degree of tissue lipidosis were recorded. In both the stilbestrol–plain mash and the stilbestrol–thyroid mash chicks, the hepatic cholesterol concentration was significantly increased about one-third above control values, with the ester fraction accounting for most of this increment (table 1). Liver phospholipids were similarily elevated. The two experimental groups had an aortic cholesterosis and lipidosis approximately equal in degree. These findings contrast with the significant differences between the 2 groups in gross pathologic grading for atheroma (see below and fig. 1).

TABLE 1.—*Mean Plasma and Tissue Lipids of Stilbestrol (Group 1), Stilbestrol-Thyroid (Group 2) and Control (Group 3) Chicks*

Group	Lipid P	Phospholipid*	Phospholipid Fatty Acid†	Total Chol.	Free Chol.	Esterified Chol.	Ratio F/T Chol.‡	Ratio: T. Chol. / Lipid P	Esterified Chol. Fatty Acid§	Total Fatty Acid	Neutral Fat Fatty Acid‖	Total Lipid (Calc.)¶
	mg. %	*mg. %*	*mg. %*	*mg. %*	*mg. %*	*mg. %*			*mg. %*	*mg. %*	*mg. %*	*mg. %*
Liver												
1	100	2600	1742	443	313	130	.71	4.4	95	4490	2653	5798
2	122	3170	2130	453	356	97	.79	3.7	71	4330	2129	5836
3	76.7	1995	1336	333	292	41	.88	4.3	30	3518	2152	4515
Aorta												
1	38.1	990	663	300	298	2	.99	7.9	0.5	—	—	—
2	37.3	970	650	274	238	36	.87	7.3	26	—	—	—
3	31.3	824	545	206	171	35	.83	6.6	26	—	—	—
Plasma—1 Week												
1	31.3	824	552	226	157	69	.68	7.3	50	—	—	—
2	13.3	346	232	101	46	55	.45	7.7	40	—	—	—
3	7.25	189	127	99	37	62	.38	13.9	45	—	—	—
Plasma—5 Weeks												
1	47.8	1245	834	474	269	205	.57	10.0	145	—	—	—
2	29.0	754	505	229	134	95	.56	9.1	69	—	—	—
3	6.17	160	107	90	31	59	.34	14.5	47	—	—	—
Plasma—27 Weeks												
1	86.0	2235	1495	775	466	309	.60	9.0	226	—	—	—
2	95.7	1490	998	751	421	330	.56	7.9	241	—	—	—
3	8.5	221	148	142	43	99	.30	16.7	72	—	—	—

Chol. = Cholesterol.

* Phospholipid = lipid P × 26.

† Phospholipid Fatty Acid = phospholipid × .67.

‡ Ratio F/T Chol. = Ratio: free cholesterol/total cholesterol.

§ Esterified Chol. Fatty Acid = Esterified cholesterol × .73.

‖ Neutral Fat Fatty Acid = Total fatty acid − (phospholipid fatty acid + cholesterol fatty acid).

¶ Total Lipid = phospholipid + total cholesterol + esterified cholesterol fatty acid + neutral fat fatty acid.

In contrast to the plasma lipid pattern, aorta cholesterol rose more than phospholipid (table 1). Hence the ratio total cholesterol/lipid phosphorus increased, whereas in the plasma it decreased. If these excess aortic lipids are derived from the hyperlipemic plasma,[15] this predominance of aortic cholesterosis over phospholipidosis may reflect a relative inability of the organism to remove cholesterol from the vessel wall.[16–18]

Morphologic findings. Grading of aortas of individual birds is presented in detail for all three groups in table 2. This data is summarized in figure 1 with the data corrected to eliminate age variations as a factor accounting for differences in pathologic findings. In contrast to the aortic lipid findings (table 1), the stilbestrol–thyroid mash chicks had a significantly lower incidence, extent and severity of gross atherosclerosis than the stilbestrol–plain mash birds. Thus only 37 per cent of the stilbestrol–thyroid mash birds (Group 2) had any gross evidence of atheroma; the average overall grading of lesions in the birds with plaques was 0.4; no birds had a grading of 1 or greater. Corresponding data for the stilbestrol–plain mash birds (Group 1) was: per cent with lesions, 67 per cent; average overall grading, 1.1; per cent with overall grading of 1 or greater, 33 per cent. The control chicks (Group 3) and the stilbestrol–thyroid mash birds (Group 2) exhibited a very similar incidence, severity and extent of atherosclerosis (figure 1). Unlike the controls, the stilbestrol–thyroid mash chicks were not entirely free of thoracic aorta lesions (table 2).

Routine microscopic sections were taken from the thoracic and abdominal aorta of chicks from each group. In general, the histologic picture of both stilbestrol-induced and spontaneous plaques was in accord with previous descriptions from this and other laboratories.[4, 8, 19, 20] Also in agreement with previous findings, two birds in Group 1 (chicks 63 and 698) without evidence of gross evidence of atheroma at twenty-seven weeks had microscopic infiltration of the intima and subjacent media with sudanophilic material. The microscopic droplets of sudanophilic material were intra- and extracellular; they were not associated with either intimal foam cell cushioning or fibrotic thickening.[4, 19] Three birds of Group 2 (chicks 283, 287 and 719) exhibited the same phenomenon. Thus both stilbestrol–plain mash and stilbestrol–thyroid mash chicks were susceptible to this diffuse microscopic lipid infiltration of the aorta. This morphologic finding correlates well with the biochemical data on

TABLE 2.—*Gross Pathologic Grading for Atheroma in Aortas and Great Vessels of Individual Birds*

Group 1					Group 2					Group 3				
Bird No.	Weeks on Diet	Grading			Bird No.	Weeks on Diet	Grading			Bird No.	Weeks on Diet	Grading		
		Thor.*	Abd.†	Sum			Thor.	Abd.	Sum			Thor.	Abd.	Sum
441	11	0	0	0	274	12	0	0	0	110	12	0	0	0
321	13	0	½	½	283	27	0	0	0	467	15	0	0	0
31	15	0	¼	¼	287	27	0	0	0	613	15	0	0	0
16	15	0	0	0	285	27	0	0	0	122	15	0	0	0
697	23	0	1½	1½	289	27	0	0	0	650	24	0	0	0
63	27	0	0	0	214	27	0	¼	¼	558	25	0	0	0
698	27	0	0	0	291	27	½	0	½	346	25	0	¼	¼
81	27	0	¾	¾	284	27	0	½	½	354	25	0	0	0
90	27	1	¾	1¾	719	27	0	0	0	681	25	0	¼	¼
85	27	0	½	½										

Group 1—Stilbestrol-implanted, plain mash fed.
Group 2—Stilbestrol-implanted, thyroid mash fed.
Group 3—Control—plain mash fed, no hormone treatment.
* Thor. = Thoracic aorta and brachiocephalic vessels.
† Abd. = Abdominal aorta and iliac vessels.

aortic lipidosis in the 2 experimental groups, and is at variance with the group differences in degree of gross atherosclerosis. The relationship of this diffuse aortic lipidosis to atherogenesis remains to be elucidated.[19, 21]

Discussion

Desiccated thyroid decreased the incidence, extent and severity of stilbestrol-induced atherosclerosis in the chick. This protective action of thyroid hormone was only partial; complete prevention of lesions was not accomplished. These findings are similar to our previous observations on the partial prophylactic effect of desiccated thyroid in chick cholesterol-induced atherosclerosis.[6, 7]

It is difficult to correlate the degree of atherosclerosis with the plasma and liver lipid levels observed in the present study. Thus the stilbestrol and the stilbestrol-thyroid treated chicks had similar lipid levels during the latter half of the experiment. Nevertheless, the stilbestrol-thyroid birds had significantly less atherosclerosis. This finding may be related to the retardation of hyperlipemia induced by thyroid during the initial weeks of the study. However, this early depression of hyperlipemia was never complete. In relation to their level of plasma lipids over the entire course of the experiment, the stilbestrol-thyroid chicks were remarkably free of lesions. Thus the possibility arises that thyroid hormone exerted its effect on atherogenesis via mechanisms other than depression of hyperlipemia.[6, 7, 22–26]

Stilbestrol-induced atherosclerosis in chicks differs from the cholesterol-induced lesion in the duration of time required for development of atheroma. Cholesterol-fed birds with a hypercholesterolemia of the same degree as stilbestrol-implanted chicks develop gross atheroma in one-third to one-half the time. Two possible explanations for this finding are suggested on the basis of present knowledge: (1) Compared to stilbestrol-implantation, cholesterol feeding probably requires the transport, turnover and metabolism of a greater load of cholesterol for a corresponding level of hypercholesterolemia[24, 26]; (2) unlike stilbestrol-implantation, cholesterol feeding induces a hyperlipemia characterized by a predominance of hypercholesterolemia over hyperphospholipemia. The ratio of cholesterol to phospholipid in the plasma rises. The opposite change is seen in the stilbestrol-treated chick. Several workers maintain that an elevated ratio plasma total cholesterol/plasma lipid phosphorus leads to lipid instability, macrochylomicronemia and atherosclerosis.[27] The predominant hyperphospholipemia of the stilbestrol-implanted chick may retard the atherogenesis presumably induced by hypercholesterolemia. However, estrogen-treated chicks eventually develop atherosclerosis. Hence it would appear that an increased ratio of total cholesterol to lipid phosphorus in the plasma is not essential for the ultimate development of atherosclerosis. Apparently atherogenesis is promoted by any derangement of lipid metabolism inducing hyperlipemia with hypercholesterolemia and an alteration of the normal quantitative relations among the plasma lipid elements.

In the present study, thyroid exhibition had a variable effect on plasma lipid levels in the stilbestrol-implanted chick. During the first weeks of the experiment, desiccated thyroid depressed hypercholesterolemia and hyperphospholipemia. This is similar to its effect in the cholesterol-fed chick.[6, 7] However, the stilbestrol–thyroid chicks eventually developed a hyperlipemia as marked as that of the birds receiving only stilbestrol. These findings are consistent with the previous observations of other workers. Thus, Fleischmann and Fried noted that thyroxine "neutralized" the effect of estradiol on serum cholesterol if equal doses of the two agents were given.[28] When estrogen dosage exceeded thyroxine dosage, hyperlipemia ensued. This situation probably obtained in our stilbestrol–thyroid chicks during the latter weeks of the present study as a result of repeated pellet implantations.

This apparent predominance of stilbestrol over thyroid was also reflected in the liver lipid pattern at the end of this study. Both the stilbestrol and the stilbestrol–thyroid treated chicks had a slight hepatic cholesterosis and phospholipidosis.[21, 22] No significant quantitative differences between the two groups were noted. Thus, at least during the latter

weeks of this experiment, thyroid was ineffective as a prophylactic lipotropic agent.[29]

The mechanisms of these hormone influences on lipid metabolism remain obscure. Fleischmann and co-workers have concluded that both stilbestrol and thyroid exert their opposing effects on plasma cholesterol concentration by shifting sterol to and from blood plasma, rather than by altering the relationship between sterol accumulation and disposal.[28, 30] Others, working with radioactive tracers, have obtained data tending to support different conclusions. Stetten has recently suggested that hyperthyroidism leads to a disproportionate increase in hepatic degradation of fat.[31] Lipid depletion results.[cf. 29, 32] Taurog et al. have shown that excised liver slices of stilbestrol-treated chicks form radiophospholipid at an enhanced rate.[33] They suggest that this is the source of stilbestrol-induced hyperphospholipemia. We have recently obtained data indicating that chronic stilbestrol administration alters the organism's overall lipid balance. In addition to hyperlipemia, the body total cholesterol, phospholipid and neutral fat increase.[14]

The interrelationships between thyroid and estrogenic hormones extend beyond lipid metabolism, and apparently operate in many physiologic situations considerably different from those of the present experiment.[34–37] Thus estrogens have been shown to suppress thyroid and plasma protein-bound iodine, probably via a pituitary action.[38, 39] The significance of these hormonal interconnections for atherogenesis remains to be elucidated.

Summary

1. Desiccated thyroid reduced the incidence and degree of stilbestrol-induced atherosclerosis in the chick.

2. During the first few weeks, thyroid hormone suppressed stilbestrol-induced hypercholesterolemia and hyperlipemia. After this period, plasma lipid levels and ratios in stilbestrol and stilbestrol-thyroid groups were essentially similar.

3. At the end of the study, both of the experimental groups had a moderate hepatic and aortic lipidosis, the degree of which in each tissue was essentially similar in each group.

4. The possible mechanisms involved in the interplay of the two hormones, thyroid and stilbestrol, in suppressing stilbestrol-induced atherosclerosis are discussed.

Acknowledgments

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Efficiency of Heparin in Retarding Media on the Maintenance of a Decreased Coagulability of the Blood

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Heparin/Pitkin menstruum has been advocated in the therapy of a variety of thromboembolic disorders. The clinical properties of two such mixtures each with and without vasoconstrictor agents is evaluated and it is demonstrated that a significant prolongation of the clotting time beyond 24 hours cannot be obtained. A comparison between the one tube and the three tube methods for the determination of the coagulation time of blood reveals that both procedures yield comparable data.

RECENT REPORTS have indicated that a Pitkin heparin menstruum can produce a consistent prolongation of the clotting time for as long as 48 hours.[1–5] During the course of studies on the effectiveness of this mixture in the therapy of myocardial infarction, we found that the duration and uniformity of action were less than that reported by others.[6] Consequently, it became necessary to re-evaluate the properties of this mixture in terms of the onset and extent of its effect on blood coagulation, as well as the duration of this action.

METHOD

Two commercially available brands* of heparin in retarding media were utilized in the present study. Brand A contained 200 mg. of the sodium salt of heparin per ml. while Brand B contained 100 mg. of the same salt per ml. Unless otherwise noted, each subject was given a single injection of an amount of menstruum which contained 400 mg. of heparin, i.e., subjects given Brand A received 2 ml. of the mixture while those given Brand B received 4 ml. of the mixture. The heparin was deposited into the deep subcutaneous tissues in the upper quadrant of the buttock through a 20 gage needle. When the injection was given, the needle was rotated so as to insure equal distribution of the menstruum.

The coagulability of the blood was determined by means of clotting times estimated by a modification of the Lee-White method. For this purpose, venepuncture was performed with a dry, sterile, 20 gage needle and a 5 ml. syringe. Two ml. of blood were withdrawn without the introduction of air into the syringe. If the vein was not cleanly negotiated, the sample was discarded. The needle was removed from the syringe, 1 ml. of blood gently expressed from the syringe and allowed to run down the side of a dry, clean test tube measuring 13 by 100 ml. The tube was then gently tilted to an angle of 90 degrees once every minute until the blood no longer ran down the side of the tube. Thereafter, the tube was progressively tilted once every minute until, at 180 degrees, no motion of the blood was noted. This was arbitrarily taken as the end point of the clotting process. The clotting time with this one tube procedure was 8.9 minutes (S.D. = ±2.2) for a group of 76 subjects.

To determine the validity of the one tube method as outlined above, 7 coagulograms were made on the bloods of 4 patients, using a three tube method similar to that outlined by Gradwohl[7] and by Loewe and Eiber.[8] One ml. of blood was expressed from the syringe into each of three test tubes. Clotting in the

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Brand A (Plain): heparin sodium, 200 mg.; sodium ethyl mercuri thiosalicylate, 0.1 mg.; gelatin, 18%; dextrose, 8%; glacial acetic acid to pH 5.6; double distilled water q.s.a.d., 1 ml.

Brand A (Vasoconstrictor): heparin sodium, 200 mg.; sodium ethyl mercuri thiosalicylate, 0.1 mg.; gelatin, 18%; dextrose, 8%; ephedrine HCl, 10 mg.; epinephrine HCl, 1 mg.; glacial acetic acid to pH 5.6; double distilled water q.s.a.d., 1 ml.

Brand B (Plain): heparin sodium salt, 200 mg.; chlorabutinol, 0.5 mg.; eucupin dihydrochloride 1 mg.; Pitkin's menstruum 2 ml.

Brand B (Vasoconstrictor): heparin sodium salt, 200 mg.; chlorabutinol, 0.5 mg.; eucupin dihydrochloride, 1 mg.; epinephrine HCl, 1 mg.; ephedrine sulfate, 25 mg.; Pitkin's menstruum, 2 ml.

first tube was determined by the method described above. One minute after obtaining the end point in the first tube, the second tube was similarly treated and thereafter the coagulability of the blood in the third tube was determined.

The subjects selected for study consisted of patients in whom there were no evidences of thromboembolic disease, heart disease, carcinoma, infections or recent operations. The subjects so selected were studied in groups designed to reveal the influence of bed rest and of the presence of a vasoconstrictor in the menstruum on the time of onset of action and duration of effect of the administration of two brands of heparin in retarding media.

Results

The clotting time as measured by the one, two and three tube procedures was determined in 4 subjects who received 7 separate injections of 400 mg. of Brand A heparin. The coagulograms thus obtained consisted of three parallel curves at each interval, when they were expressed in terms of the absolute clotting time. The clotting time obtained by the three tube method was greater than that obtained with the use of two tubes, while that derived by the one tube method always gave the shortest clotting time. This relationship was found to be true for the pre-injection clotting times of blood as well as for those blood samples drawn after the injection of heparin. When the data were expressed as the per cent change from the pre-injection clotting times, essentially similar results were obtained by the use of one, two or three tubes.

An analysis of variance[8] revealed that the differences between data obtained by the procedure using one, two or three tubes as outlined above were not significant at any of the intervals. The apparently greater effect noted at 6 hours with the one tube method could not be distinguished statistically from that obtained by use of the other two tubes. Therefore, any of the three tubes yields comparable information in regard to the percentage increase in clotting time during heparin therapy. This point is of some practical importance since it validates the use of the one tube procedure and thus decreases the absolute time required for a determination of the clotting time of blood (fig. 1).

A total of 82 coagulograms were obtained from 76 subjects. The data obtained after various treatments are summarized in table 1. In order to determine the effect of bed rest or activity on the action of heparin in retarding media, Brand A heparin without vasoconstrictor was administered to ambulatory subjects (group 1) and to patients confined to bed for the purposes of this study (group 2). The 17 coagulograms on the ambulatory subjects and 20 coagulograms on the subjects at bed rest are essentially the same (table 1). Since no statistically significant difference could be demonstrated between the data obtained from both groups at various intervals, it may be anticipated that the use of repository heparin in ambulatory patients will yield data similar to that obtained in patients who are immobilized and confined to bed.

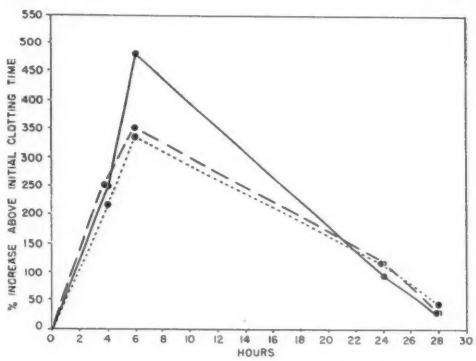

FIG. 1. Percentage increase over initial values of the clotting time in each of three tubes. Tube 1, solid line; tube 2, broken line; tube 3, dotted line.

In order to compare the two brands of heparin, coagulograms obtained after the administration of Brand A (group 2) were compared with the data obtained from subjects injected with Brand B (group 3). Twelve of the 14 subjects in group 3 were also utilized to determine the effect of Brand A. The administration of Brand B preceded the administration of Brand A by at least 48 hours in six of these subjects, while the administration of Brand B followed the administration of Brand A by at least 48 hours in the others. An analysis of the data obtained in this manner revealed that the two brands are essentially similar in their effect on the prolongation of clotting times. When

TABLE 1.—*Effect of Various Types of Heparin in Retarding Media on Clotting Time of Blood*
(Hours after Injection)

GROUP	NUMBER OF PATIENTS	0	1	4	6	8	12	16	18	20	24	28	30	32
1 Brand A Plain—400 mg.	11	[17] 8.8 ±1.8	[6] 10.8 ±2.2	[11] 30.4 ±11.4	[11] 40.3 ±11.4				[6] 20.7 ±8.8		[17] 11.6 ±7.3			
2 Brand A Plain—400 mg.	20	[20] 9.3 ±2.7	[7] 12.6 ±7.7	[19] 34.6 ±17.3	[8] 49.4 ±11.2	[10] 33.4 ±12.1	[10] 37.2 ±11.6	[9] 32.9 ±11.4		[7] 24.7 ±8.6	[17] 14.8 ±5.9	[5] 11.2 ±6.3		
3 Brand B Plain—400 mg.	14	[14] 9.3 ±2.0		[14] 39.3 ±8.7	[10] 54.6 ±8.9	[4] 37.5 ±9.3	[4] 21.7 ±6.0	[4] 22.5 ±5.9		[4] 17.5 ±4.1	[13] 11.9 ±5.6			
4 Brand A Vasoconstrictor—400 mg.	17	[17] 8.7 ±2.6		[17] 16.2 ±8.8	[12] 20.1 ±2.9	[5] 12.6 ±2.9	[5] 18. ±4.8	[5] 43.8 ±10.5		[5] 35.8 ±0.9	[16] 21.6 ±11.3	[11] 14.3 ±8.3	[5] 15.8 ±6.4	
5 Brand B Vasoconstrictor—400 mg.	9	[9] 7.8 ±1.6		[9] 10.6 ±2.6	[9] 12.9 ±4.0						[9] 20.7 ±11.4		[5] 9.8 ±2.8	
6 Brand A Plain—200 mg. Vasoconstrictor—200 mg.	5	[5] 9.8 ±1.4		[5] 16 ±2.1		[5] 21 ±1.3	[5] 33.4 ±4.8	[5] 46.6 ±9.7		[5] 49.2 ±2.7	[5] 28.3 ±4.1	[5] 20.8 ±3.		[5] 14.8 ±3.2

Number of determinations at each interval indicated in brackets. Clotting time in minutes (mean ± standard deviation).

either brand of heparin was administered, a rapid and progressive increase in the clotting time was noted which by the end of four hours was three times that of the pre-injection level. The peak of the heparin effect was reached 6 hours after injection. From 18 to 20 hours after the injections the clotting time of the blood remained between two to four times that before the injection of heparin. Thereafter, a progressive decline in clotting time occurred so that by the end of 24 hours after the injection of either Brand A or B, there was no statistically significant deviation from the pre-injection clotting time.

Of interest is the fact that five of the 20 subjects who received Brand A complained of pain at the site of the injection; 2 of these developed hematomata. Eight of the 14 patients receiving Brand B complained of local pain; one of these developed a hematoma.

In order to determine the effect of the inclusion of a vasoconstrictor in the menstruum, coagulograms were obtained on patients injected with Brand A containing vasoconstrictor (group 4) and on patients injected with Brand B containing vasoconstrictor (group 5). In eight instances, the same subjects were utilized to test the action of the two brands and in such instances, at least 48 hours intervened between injections.

The data summarized in table 1 reveal that the action of the two brands containing vasoconstrictor is essentially similar. Although the increase in clotting time appeared to occur at a more rapid rate with Brand A than with Brand B, students' "t" test[8] showed that the difference between the effect of the two brands is insignificant. Twenty-four hours after the injection of both brands, the clotting time was approximately two and one-half times greater than the initial time, but by 30 hours after the injections the clotting time had approached the pre-injection clotting times in both groups. Five of the 17 patients injected with Brand A complained of pain as did also 2 of the 9 patients injected with Brand B. No significant alterations in the blood pressure or heart rates were noted during the performance of the tests.

The incorporation of a vasoconstrictor agent in the menstruum definitely prolongs the duration of the decreased coagulability of the blood as compared with the effect of a similar preparation of heparin containing no vasoconstrictor agent (fig. 2). It is evident, however, that the decreased coagulability of the blood does not reach the so-called therapeutic levels as rapidly as does the heparin menstruum containing no vasoconstrictors. Consequently, despite the apparent increase in the duration of the effect induced by heparin containing vasoconstrictors, the actual duration of a therapeutically effective hypocoagulability is not maintained for more than 16 hours.

It has been suggested that an effective prolongation of the clotting times may be attained

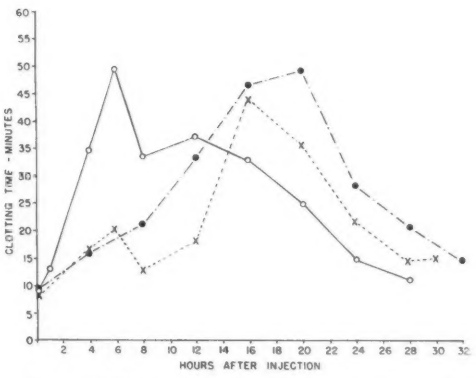

FIG. 2. Effect of 400 mg. of heparin in retarding media on the coagulation time of blood.

o—o, heparin, plain; x - - - x, heparin, vasoconstrictor; ● — · — ●, heparin, half plain, half vasoconstrictor.

by simultaneous injection of two types of heparin mixtures, i.e., of a heparin mixture with, and one without, vasoconstrictor.[1–5] Accordingly, we tested this hypothesis by administering an injection of 200 mg. of Brand A without vasoconstrictor in one buttock and a simultaneous injection of 200 mg. of Brand A with vasoconstrictor in the other buttock of each of five subjects (group 6). The coagulability of the blood was determined at four-hourly intervals after the injections. A significant prolongation of the clotting time was first noted 8 hours after injection; this persisted for 28 hours and began to approach the pre-injection coagulability by the end of 32 hours (table 1).

It is evident from figure 2 that before the eighth hour after injection there was very little difference between the action of the mixture of heparin with and without vasoconstrictor agents on the one hand (group 6) and that of the heparin containing only vasoconstrictors (group 4) on the other. At the twentieth hour after injection, the prolongation produced in group 6 is somewhat greater than that in group 4 but thereafter the differences are not statistically significant.

Discussion

The responses of a group of subjects to any pharmacologic agent will tend to fall along a normal distribution curve. For that reason, fluctuations in the degree of effect of the same type of heparin were anticipated and, as a matter of fact, were noted from patient to patient. The mean responses of the groups, however, represent the type of result that can be expected from the administration of the several types of heparin to large groups of subjects.

These studies do not confirm the contention that an effective decrease in the coagulability of the blood for from 36 to 48 hours results from the single injection of a heparin menstruum.[1–5] Further, the incorporation of vasoconstrictor agents in the menstruum merely delays the onset of the effect and does not prolong the duration of the therapeutically effective decrease in the coagulation of the blood (fig. 2).

Since the administration of repository heparin results in a relatively rapid decrease in the coagulability of the blood while the action of heparin mixtures containing vasoconstrictors results in a prolongation of the effect once it appears, it was postulated that the simultaneous administration of these two mixtures of heparin might prove more effective than the injection of either alone. The data obtained with group 6 reveal that the above does not occur. Whether the failure to obtain a rapid development of the heparin effect was due to the use of only one-half the quantity of plain heparin in retarding medium was not determined. The lack of any evidences of a systemic effect of the vasoconstrictors makes it improbable that such an effect played a role in delaying the rate at which the heparin was absorbed from the contralateral side.

Loewe and his associates have postulated[1–4] that patients with thrombophlebitis usually require only 300 mg. of a mixture of plain heparin and that containing vasoconstrictors, whereas those with coronary thrombosis usually require 400 mg. of the preparation without vasoconstrictor in order to maintain effective therapeutic levels. For such reasons we employed the higher dosage of heparin in the present study. Consequently, the discrepancy between the data reported herein and those of Loewe cannot be attributed to an insufficient dosage. Since we found no essential differences between the two commercially available brands of heparin, the discrepancy cannot be attributed to differences in the composition of the menstruums.

It would appear from our data that to maintain an effective diminution of the coagulability of the blood, injections of heparin in retarding media should be made at more frequent intervals than 32 to 48 hours. Such a conclusion is inherent in the recent studies of DeTakats[5] who utilized a different method to measure the coagulability of the blood and obtained data essentially similar to that reported herein.

Summary and Conclusions

1. Estimation of the clotting time of the blood by means of either the one tube or three tube procedure yields values which are comparable when the clotting time is expressed in terms of the percentage increase above the initial level.

2. The effect of heparin in retarding media is not influenced by bed rest since similar changes in the coagulability of the blood are induced in subjects who are ambulatory as well as those confined to bed.

3. Evidence could not be obtained that the single injection of various types of heparin in retarding media is effective in maintaining a decreased coagulability of the blood for more than a twenty-four hour interval.

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The Metabolism of Lactate and Pyruvate in Children with Congenital Heart Disease

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with the technical assistance of Katharine S. Gullixson

Venous blood lactic acid and pyruvic acid concentrations and lactate-pyruvate ratio were studied in 42 normal adults, 16 normal children and 18 children with congenital heart disease. There was elevation of resting values in children as compared with adults, but no significant change of values of resting children with congenital heart disease as compared with normal children. Following a standard exercise test, children with patent ductus arteriosus showed a time curve comparable to normal children, but children with cyanotic heart disease showed a persisting elevation of all values. The lactate-pyruvate ratio varied inversely with calculated mean capillary blood pO_2.

PATIENTS with congenital heart disease should be excellent subjects for evaluation of the metabolic effects of chronic hypoxemia. Direct measurements of the arterial blood oxygen tension of 30 individuals with tetralogy of Fallot show a range of 30.2 to 66.0 mm. Hg,[1] values significantly lower than recently reported arterial pO_2 figures for normal individuals. Although the work of Bing and associates[1] would indicate that certain mechanisms reduce the gradient of fall between arterial blood pO_2 and mean capillary blood pO_2, the application of the formula of Barcroft for the approximation of "mean capillary pO_2" to Bing's crude data shows a significant reduction of mean capillary blood pO_2 of the cyanotic patients in Bing's series as compared with normal individuals. Such a reduction provides sufficient stimulus to the tissues to produce an increased concentration of hemoglobin in the circulating blood. The question arises whether or not such chronic hypoxemia results in alteration of mechanisms other than the oxyhemoglobin transport system.

One of the most noticeable accompaniments of acute hypoxia is the accumulation of lactic acid in the blood. Energy for the synthesis of high energy phosphate bonds during the glycolytic phase of carbohydrate breakdown is supplied largely by the reactions involved between 1,3-diphosphoglyceraldehyde and pyruvic acid.[2] During the conversion of 1,3-diphosphoglyceraldehyde to 1,3-diphosphoglyceric acid, diphosphopyridine nucleotide (coenzyme I) is reduced, and to maintain the conversion adequate amounts of the oxidized nucleotide must be provided continually. In the presence of sufficient amounts of oxygen, the reduced diphosphopyridine nucleotide formed in this reaction is reoxidized through the cytochrome system. In the absence of adequate oxygen concentrations reoxidation is accomplished by pyruvic acid, the latter being reduced to lactic acid. The ratio of the concentrations of lactate and pyruvate in the circulating blood reflects the degrees to which the reoxidation of diphosphopyridine nucleotide is progressing through the aerobic cytochrome system and through the anaerobic lactate-pyruvate system. With significant reduction of oxygen concentration, a greater fraction of the total diphosphopyridine nucleotide oxidation is accomplished by pyruvate, causing an increase in blood lactate and in the blood lactate to pyruvate ratio (L-P ratio). The reaction, pyruvate $\rightleftarrows$ lactate, is catalyzed by the enzyme, lactic dehydrogenase.

Friedemann and Barborka[3] found that, in the blood of normal adults during exercise, there is a rise of both lactate and pyruvate

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concentrations, the lactate concentration rising more rapidly with consequent elevation of the lactate-pyruvate ratio early following the exertion. They demonstrated that changes in the rate of fall of the lactate-pyruvate ratio followed changes in pulse rate and respiratory rate. They concluded that following exercise the lactate-pyruvate ratio was an indicator of the return of adequate tissue oxygenation. Tepperman and Tepperman[4] showed that there was elevation of the blood lactate-pyruvate ratio of normal individuals exercising while breathing air under reduced barometric pressure. The elevation of the lactate-pyruvate ratio observed at a simulated altitude of 5000 feet was suppressed by breathing 100 per cent oxygen at that altitude.

The lactate-pyruvate ratio has not been studied heretofore under the conditions prevailing in children with congenital heart disease.

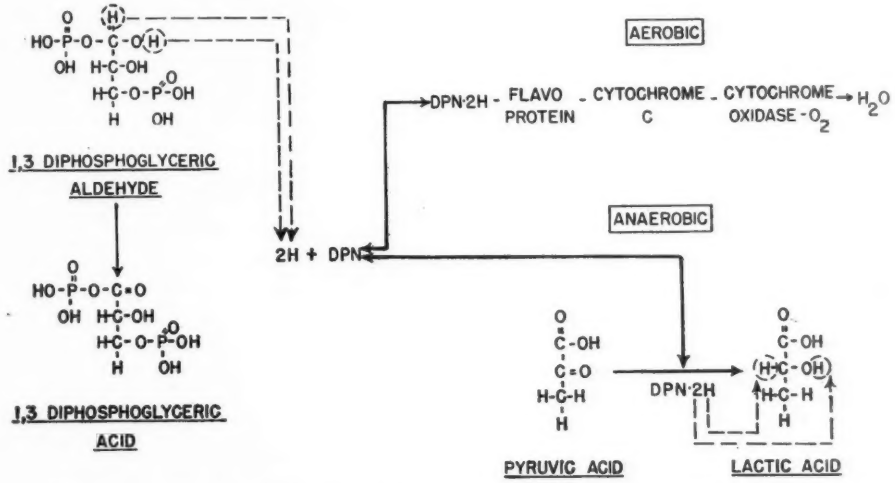

FIG. 1. Diagrammatic illustration of the alternative pathways for the maintenance of oxidized diphosphopyridine nucleotide (Coenzyme I, DPN): aerobically through the cytochrome-oxidase system, anaerobically through the pyruvate-lactate conversion system.

EXPERIMENTAL

Values first were established for the venous blood lactate concentration, pyruvate concentration, and lactate-pyruvate ratio in 42 normal adults and in 16 normal children. The normal children included patients hospitalized but ambulatory and afebrile. These children were usually late convalescents after elective surgical operations. There was no significant difference between the values for the hospitalized children in this group, and the values observed in several well children attending the outpatient clinic as tuberculosis contacts.

The children with congenital heart disease were studied under hospital conditions. The diagnosis of congenital heart disease, cyanotic and acyanotic, was made by the usual clinical and laboratory evidences of heart disease. In most instances the anatomic lesion was confirmed at the time of surgery or autopsy, or by the corollary evidence of improvement of cyanosis following the Blalock-Taussig operation. The acyanotic type of congenital heart disease was represented exclusively by patients with patent ductus arteriosus. The cyanotic group consisted predominantly of children with the tetralogy of Fallot.

Methods

Blood samples were drawn from an antecubital vein whenever possible. In some of the younger children it was necessary to use the femoral vein, or rarely, the external jugular vein. During serial sampling for the exercise

test, the arm veins were used exclusively. Use of a tourniquet was necessary in order to obtain blood samples rapidly from the children. The tourniquet was kept in place as short a time as possible and, where feasible, released after entry into the vein with a short waiting period prior to withdrawal of the blood. No systematic differences were observed using this tourniquet technic alternately in 15 adults (table 2). Arterial blood samples were drawn from the femoral vessels. Uncalibrated 10 ml. syringes were used for sampling. After ejecting any foam present in an 8–10 ml. sample, a portion of the blood was delivered under oil into an oxalate-fluoride tube. Ejection of blood from the syringe was stopped exactly at the 5.2 ml. mark. Five milliliters of blood were delivered through the needle into 10 ml. of freshly prepared 20% trichloracetic acid. This technic permitted rapid deproteinization immediately interrupting glycolysis. Blood samples were drawn 2–4 hours after the last meal (breakfast or lunch) and analyzed the same day.

The standard exercise test of Cournand and Richards[5] was used. During this test the patient steps up and down from a stool 20 cm. high 30 times in one minute.

Lactate and Pyruvate. The deproteinized blood sample was centrifuged at 2000 r.p.m. for 10 minutes. Lactate concentration was determined on duplicate 3 ml. aliquots of the supernate by the method of Long.[6] It was found that the blank recommended by Long was not necessary in our application of the method, probably due to the fact that we have used a 10% solution of reagent grade ceric sulfate rather than the 30% solution of 35% pure ceric sulfate employed by Long. Pyruvate concentration was determined on duplicate 1.5 ml. aliquots of the supernate by the method of Friedemann and Haugen.[7] During these experiments 142 blood samples were analyzed. The maximum difference between duplicate analyses was 2.7 mg. lactate per 100 ml. blood and 0.10 mg. pyruvate per 100 ml. blood. For lactate, the average difference between duplicate determinations was 1.55 mg. (standard deviation 0.572 mg.). The average difference between duplicates for pyruvate was 0.034 mg. (standard deviation 0.032 mg.).

Carbon dioxide and oxygen content were determined on single one milliliter samples of the blood under oil by the method of Van Slyke and Neill.[8] Oxygen capacity was determined after equilibration of blood with air at room temperature in a tonometer.

Blood lactic dehydrogenase. The lactic dehydrogenase content of erythrocytes was estimated by a quantitative application of the ferricyanide method for the study of dehydrogenase systems.[9] In a bicarbonate medium the reduction of ferricyanide by the hydrogen activated through the dehydrogenase system gives rise to equimolar amounts of carbon dioxide. (The use of ferricyanide as a hydrogen acceptor has the advantages of nontoxicity and nonautooxidizability).

The evolution of carbon dioxide was measured in the Barcroft-Warburg manometric apparatus at a temperature of 38 C. with an oscillation rate of 120 cycles per minute. The reaction cell of the flask contained 3 ml. of a solution of the following composition: sodium bicarbonate, 0.05 M; sodium lactate pH 7.4, 0.10 M; sodium cyanide pH 7.4, 0.05 M; diphosphopyridine nucleotide, 0.0012 M*; lysed erythrocytes, 0.20 ml.

Sodium cyanide was used to fix the pyruvate produced in the reaction by conversion to the pyruvate cyanohydrin. The final pH of this solution was 7.4 at 38 C. in the gas medium of 90% nitrogen 10% carbon dioxide. Blood containing not more than 2 mg. of potassium oxalate per ml. was centrifuged and the packed cells washed three times with an equal volume of 0.9% sodium chloride solution, the last centrifugation being carried out at 2000 r.p.m. for 10 minutes. The cells then were laked in 5 volumes of distilled water. The diphosphopyridine nucleotide was reported to be 60% pure by spectrophotometric analysis by the manufacturers. The side arm of the flask contained 0.2 ml. of 10 per cent sodium ferricyanide in 0.05 M sodium bicarbonate. A small square of yellow phosphorus was placed in the center well to eliminate traces of oxygen.

* Nutritional Biochemicals, Inc., Cleveland, Ohio

Following gas and temperature equilibration of the reaction manometers, ferricyanide was tipped into the reaction cell and gas evolution measured for 30 minutes at five minute intervals. Rate of evolution of carbon dioxide during this period was expressed as microliters of carbon dioxide (STPD) produced in nitrogen per hour ($Q_{CO_2}^{N_2}$). Determinations were run in duplicate.

Lactic Dehydrogenase Index = $(Q_{CO_2}^{N_2}) \times$ (*Cell volume*)

expressing a figure proportional to the dehydrogenase activity of undiluted whole blood.

Results

Table 1 lists the concentrations of blood lactate and blood pyruvate and the L-P ratio in 16 normal children at rest. Significant differences for any of these values were not found between the 8 males and 8 females, or between the group of 11 children who did not cry or struggle during the blood sampling and the group of 5 children who cried and/or struggled to a varying degree. Table 2 summarizes similar data obtained in 42 normal adults. There was no significant difference between the 32 adult males and 10 adult females.

TABLE 1.—*Normal Children*

Name	Age	Sex	Cooperation	Lactate mg. per 100 ml. blood	Pyruvate mg. per 100 ml. blood	L-P Ratio
H. O.	7	M	Good	9.97	0.76	13.0
C. K.	13	F	Good	14.60	1.24	11.8
L. L.	4	F	Poor	13.12	1.29	10.2
C. H.	3	F	Poor	17.55	1.43	12.3
G. R.	6	M	Good	12.40	1.15	10.8
V. R.	4	F	Good	20.50	1.67	12.3
E. R.	4	M	Poor	18.11	1.56	11.6
L. W.	12	M	Good	11.93	1.04	11.5
H. B.	10	M	Good	12.04	1.04	11.6
D. E.	6	M	Poor	12.04	1.18	10.2
R. M.	13	M	Good	17.64	1.39	12.7
K. C.	6	F	Good	13.50	0.97	13.9
C. O.	7	F	Good	11.93	1.04	11.5
W. S.	12	F	Good	15.19	1.04	14.6
D. L.	11	M	Poor	15.08	1.22	12.3
D. H.	6	F	Good	14.30	1.50	9.5
Average and Standard Deviation (16 children)				14.37 ± 2.75	1.22 ± 0.26	11.86 ± 1.28
Average and Standard Deviation						
Males (8 children)				13.65 ± 2.95	1.17 ± 0.25	11.71 ± 1.21
Females (8 children)				15.09 ± 2.74	1.27 ± 0.28	12.01 ± 1.70
p for Difference*				$0.4>p>0.3$	$0.5>p>0.4$	$0.3>p>0.2$
Average and Standard Deviation						
Good Cooperation (11 children)				14.00 ± 2.44	1.17 ± 0.26	12.01 ± 1.63
Poor Cooperation (5 children)				15.38 ± 2.65	1.34 ± 0.16	11.32 ± 1.06
p for Difference				$0.4>p>0.3$	$0.3>p>0.2$	$0.5>p>0.4$

* Standard statistical methods are used. The value p is derived from tables of t and indicates the probability that an observed difference is due solely to samping error. If p is 0.05 or less, the observed difference is considered statistically significant. The high values of p may be regarded as evidence of agreement between the groups.

The stated concentration of diphosphopyridine nucleotide approached complete saturation of the reaction. The rate of carbon dioxide evolution was not linear during the 30 minute period. Variations in cyanide concentration did not affect the nonlinearity of gas evolution.

Cell volume determinations were made by centrifuging oxalated blood to a constant red cell volume in a Wintrobe blood volume index tube. The value, *lactic dehydrogenase index*, was calculated by the formula:

The values for lactate concentration, pyruvate concentration, and lactate-pyruvate ratio

were significantly higher in children than in the adults.

	Lactate mg. per 100 ml. blood	Pyruvate mg. per 100 ml. blood	L-P Ratio
1. Normal adults	9.36	1.03	9.10
2. Normal children	14.37	1.22	11.86
p difference	<0.001	<0.001	<0.001

The results relating to blood lactate and pyruvate and the L-P ratio obtained in 8 children with acyanotic congenital heart disease and 10 children with cyanotic congenital heart disease at rest are given in tables 3 and 4. There is no significant difference between the values for children with congenital heart disease and those obtained in normal children.

Results obtained from the Cournand-Richards standard exercise test in 7 normal children, 6 children with acyanotic congenital heart disease and 3 children with cyanotic congenital heart disease are summarized in figure 2.

The differences observed between the normal and acyanotic children were not statistically significant, suggesting normal exercise tolerance in children with patent ductus arteriosus. The cyanotic children showed reduced exercise tolerance clinically, and a significant elevation of lactate-pyruvate ratio immediately and 15 minutes after exercise.

In order to determine the correlation between the L-P ratio and the degree of oxygenation of tissue, the L-P ratio was plotted against approximated mean capillary pO_2. The approximation of mean capillary pO_2 requires several assumptions due to the lack of knowledge concerning the quantitative aspects of oxygen diffusion in the capillaries and lack of knowledge concerning the nature of the oxyhemoglobin dissociation curve of individuals with congenital cyanotic heart disease. A modification of the formula of Barcroft was used

TABLE 2.—*Normal Adults*

	Lactate mg. per 100 ml. blood	Pyruvate mg. per 100 ml. blood	L-P Ratio
Average and Standard Deviation (42 adults)	9.36 ± 1.62	1.03 ± 0.15	9.10 ± 1.20
Males (32 adults)	9.38 ± 1.77	1.05 ± 0.17	8.93 ± 1.42
Females (10 adults)	9.29 ± 1.76	0.97 ± 0.15	9.48 ± 0.96
p for Difference	$p>0.9$	$0.2>p>0.1$	$0.3>p>0.2$
With Tourniquet (8 adults)	10.02 ± 1.09	1.14 ± 0.14	8.91 ± 1.21
Without Tourniquet (7 adults)	10.16 ± 0.67	1.12 ± 0.13	9.17 ± 1.39
p for Difference	$p>0.9$	$0.8>p>0.7$	$p>0.9$

TABLE 3.—*Children with Patent Ductus Arteriosus*

Name	Age	Sex	Lactate mg. per 100 ml. blood	Pyruvate mg. per 100 ml. blood	L-P Ratio
J. C.	3	M	16.61	1.22	13.61
S. S.	8	F	15.86	1.50	10.57
E. C.	4	F	15.75	1.84	8.56
H. H.	12	F	15.06	1.25	12.05
A. W.	10	F	15.53	1.39	11.18
L. C.	5	F	11.36	1.01	11.25
D. F.	14	F	11.97	0.97	12.34
J. S.	12	F	11.00	1.08	10.19
Average and Standard Deviation (8 children)			14.14 ± 2.35	1.28 ± 0.27	11.24 ± 1.57
Average for Normal Children (Table 1)			14.37 ± 2.75	1.22 ± 0.26	11.86 ± 1.28
p for Difference			$0.9>p>0.8$	$0.8>p>0.7$	$0.4>p>0.3$

TABLE 4.—*Lactate, Pyruvate and L-P Ratio in Children with Cyanotic Congenital Heart Disease*

Name	Age	Sex	Diagnosis	Lactate mg. per 100 ml. blood	Pyruvate mg. per 100 ml. blood	L-P Ratio
M. B.	3	M	Tetralogy of Fallot	20.43	1.56	13.10
C. B.	12	M	Truncus arteriosus; cor triloculare	10.53	0.94	11.20
T. M.	5	M	Tetralogy of Fallot	14.62	1.36	10.75
K. C.	1	F	Probable tetralogy of Fallot	41.65	3.41	12.21
L. K.	4	M	Probable tetralogy of Fallot	15.08	1.38	10.93
J. S.	6	M	Tetralogy of Fallot and patent ductus arteriosus	10.35	1.04	9.95
C. L.	4	M	Unknown	13.28	1.29	10.29
S. S.	5	M	Tetralogy of Fallot	16.54	1.29	12.82
G. S.	9	M	Unknown	14.69	1.50	9.80
C. E.	7	M	Tetralogy of Fallot	15.19	1.18	12.87
Average and Standard Deviation (10 children)				17.24 ± 8.65	1.50 ± 0.68	11.38 ± 1.20
Average for Normal Children (Table 1)				14.37 ± 2.75	1.22 ± 0.26	11.86 ± 1.28
p for Difference				$0.3>p>0.2$	$0.2>p>0.1$	$0.4>p>0.3$

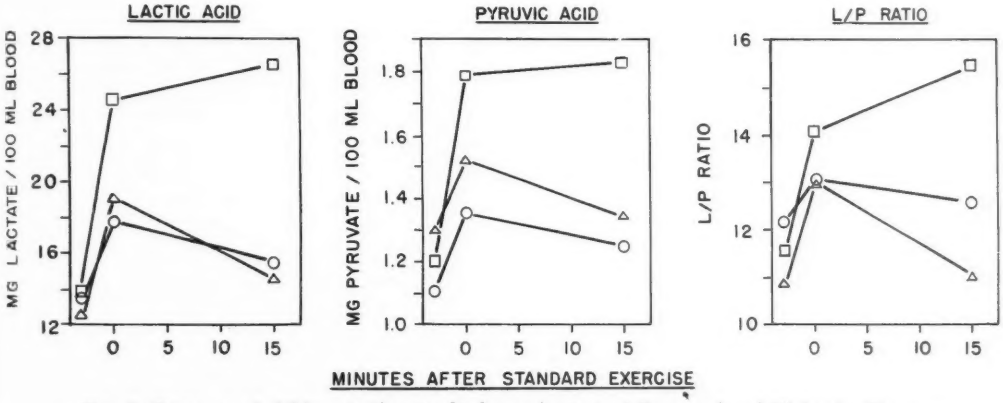

FIG. 2. Response of children to the standard exercise test of Cournand and Richards. Observations were made at rest, immediately prior to exercise, immediately following the exercise, and 15 minutes following the completion of the exercise. ○, mean values of seven normal children; △, mean values of six children with patent ductus arteriosus; □, mean values of three children with cyanotic congenital heart disease.

for the approximation of mean capillary oxygen tension in the region drained by the cognate arm vein:

$$Mean\ Capillary\ pO_2 = Venous\ pO_2 + \frac{(arterial\ pO_2 - venous\ pO_2)}{3}$$

In the absence of any observations of arterial oxygen saturation or pO_2 in the normal and acyanotic groups, an arterial pO_2 of 88 mm. Hg was assumed. The other pO_2 values were determined by plotting from a standard oxyhemoglobin dissociation curve, pH 7.4, using observed oxyhemoglobin saturation values. The assumption must be made that the blood of patients with cyanotic congenital heart disease conforms to the pH 7.4 oxyhemoglobin dissociation curve in the face of a plasma ionic

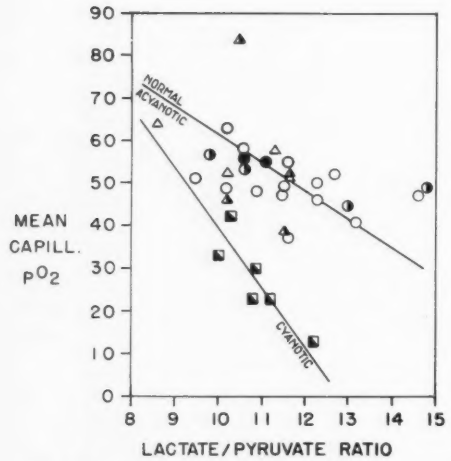

FIG. 3. Relation of calculated mean capillary pO_2 and lactate-pyruvate ratio as measured by analysis of cubital vein blood. ○, normal children at rest; ●, normal children immediately following Cournand-Richards standard exercise; ◑, normal children 15 minutes after completion of standard exercise; △, children with patent ductus arteriosus at rest; ▲, children with patent ductus arteriosus 15 minutes after completion of standard exercise; ◪, children with cyanotic congenital heart disease at rest. Regression lines were fitted by the least squares method.

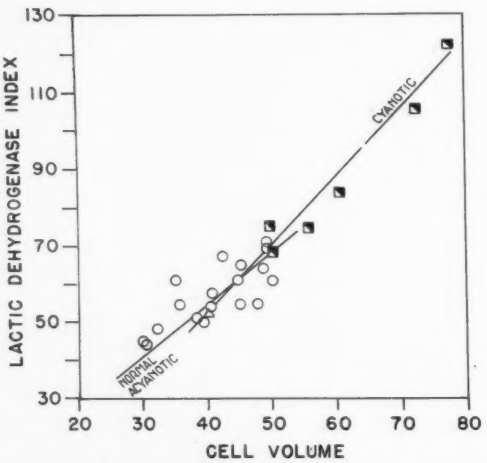

FIG. 4. Relation of lactic dehydrogenase index and hematocrit of venous blood. ○, 9 normal adults and 8 normal children (age range 2 years to 32 years); △ child with patent ductus arteriosus; ◪, 4 children and 2 adults with congenital cyanotic heart disease. Regression lines were fitted by the least squares method.

structure resulting in a normal plasma pH but a significantly lowered plasma pCO_2. This assumption is made on the evidence of Bing's direct measurements of blood oxygen saturation and pO_2.[1] These direct values clump around the pH 7.4 standard oxyhemoglobin dissociation curve.

Figure 3 is a graph of the lactate-pyruvate ratio plotted against mean capillary pO_2 in 31 observations on 29 individuals.

The normal and acyanotic values seem to fit a straight regression line and, by the least squares method, the regression equation, $pO_2 = 128 - 6.76$ L-P ratio, is derived. However there is a wide range of estimating error about this line as indicated by a standard deviation of established pO_2 points about the line of ± 9.78 mm. pO_2. The correlation coefficient is -0.64, which is significantly different from zero ($p < 0.01$). There appears to be better correlation between pO_2 and L-P ratio in the 6 cyanotic children ($r = -0.87$, $p < 0.05$) but the small sample size excludes more extensive statistical analysis.

Blood of the cyanotic children has a higher lactic dehydrogenase enzyme activity by virtue of an increased concentration of red blood cells, there being no significant alteration of the enzyme concentration per unit volume of red cells (fig. 4).

DISCUSSION

The demonstration that the L-P ratio in children with cyanotic congenital heart disease at rest does not differ from that of normal children suggests that oxygen requirements are being met under such conditions. It is evident, however, that the existing balance can be upset easily, as the data from the standard exercise test demonstrate. In normal children and in those with patent ductus arteriosus, the lactate, pyruvate and L-P ratio values, rising following exercise, had returned to levels not significantly different from the resting values 15 minutes following exercise. In the children with cyanotic congenital heart disease, the changes were not only more marked just following exercise but persisted 15 minutes later.

The inverse correlation observed between the L-P ratio and mean capillary pO_2 demon-

strates further the relation of this value to tissue oxygenation. The fact that children with cyanotic congenital heart disease have a normal L-P ratio in spite of a reduced mean capillary pO_2 is good evidence that compensatory mechanisms exist through which such individuals maintain normal oxidative conditions in their tissues at rest.

Recent studies indicate that chronic anoxia does not produce significant elevation of iron-porphyrin compounds other than hemoglobin. Drabkin[10] has shown that the rate of appearance of new cytochrome in regenerating rat liver is unchanged under conditions of chronic anoxia. The myoglobin concentration in skeletal muscle of rats[11] and dogs[12] remains unchanged after prolonged exposure to barometric pressure reduced sufficiently to produce marked polycythemia. Changes in these and other tissue constituents might occur under conditions of chronic anoxia but a simpler explanation can be advanced. It is known that oxygen requirements often are reduced significantly in cyanotic congenital heart disease. Bing[13] reports a series of cyanotic patients in whom the basal metabolic rate averaged −24 per cent. The ability of cyanotic individuals to maintain a normal L-P ratio may be related to this observation of a lowered metabolic rate. The difference observed between the L-P ratio in resting normal children and resting normal adults is of interest in this regard. Standard tables for the basal metabolic rate indicate that the value for normal children is 26 per cent higher than the value for normal adults in the age groups of this series. The L-P ratio was increased 29 per cent in the normal children here as compared with the normal adults, suggesting a possible correlation between basal metabolic rate and the L-P ratio. The existence of a normal L-P ratio in the presence of a presumably reduced basal metabolic rate in the patients of the cyanotic group suggests that, due to the hypoxic conditions, the L-P ratio is elevated relative to the basal metabolic rate. Direct comparisons between L-P ratio and the rate of oxygen consumption in cyanotic children and hypothyroid acyanotic individuals should resolve this aspect of the problem.

Krogh[14] calculated the capillary-cell pO_2 difference necessary to produce a diffusion gradient sufficient to maintain the observed oxygen consumption of mammalian muscle at rest and arrived at a range, 19–49 mm. Hg. The reduction of mean capillary pO_2 in cyanotic congenital heart disease to a range in Bing's series of 24.8–45.4 mm. Hg and in our series a range of 13–42 mm. Hg presents the possibility that the rate of oxygen diffusion may limit the rate of its uptake under such conditions of chronic anoxia and lead to a lowered metabolic rate.

In the face of normal lactate and pyruvate concentrations the normal lactic dehydrogenase assay would indicate that, at least within the red blood cell, there is no increase in the rate of pyruvate-lactate conversion. The findings indicate association between erythrocyte metabolism and the lactic dehydrogenase system, (possibly the maintenance of the iron of hemoglobin in the ferrous state[15]).

Summary

1. Blood lactate and pyruvate concentrations and lactate-pyruvate ratio values are established for normal adults and normal children. The resting values are significantly higher in children than in adults.

2. Children with acyanotic congenital heart disease have a normal lactate-pyruvate ratio at rest. Children with cyanotic congenital heart disease have a normal resting lactate-pyruvate ratio in spite of a lowered mean capillary oxygen tension. The possibility is presented that the normal lactate-pyruvate ratio in these children is related to their low metabolic rate.

3. The lactate-pyruvate ratio varies inversely with calculated mean capillary oxygen tension at rest and after exercise.

4. There is a delayed return of the lactate-pyruvate ratio to normal following exercise in children with cyanotic congenital heart disease.

Acknowledgments

We are indebted to Dr. Edward S. West for advice and to Dr. Carl E. Hopkins for guidance during statistical analysis of the data.

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Pathology of the Pulmonary Vascular Tree

I. A Comparison of the Intrapulmonary Arteries in the Eisenmenger Complex and in Stenosis of Ostium Infundibuli Associated with Biventricular Origin of the Aorta

By W. Harold Civin, M.D., and Jesse E. Edwards, M.D.

The case to be reported is characterized by stenosis of the ostium infundibuli of the right ventricle and biventricular origin of the aorta. Certain of the anatomic features of the heart in this case are similar to those of the Eisenmenger complex. One difference between the two conditions is that in the case herewith reported subpulmonary (infundibular) stenosis existed, while in the Eisenmenger complex there is no anatomic barrier to pulmonary blood flow, either in the heart or great vessels. On these gross anatomic differences seem to depend the differences in structure of the intrapulmonary arteries in the two conditions.

A SIMILARITY to Eisenmenger complex was noted in certain of the anatomic features of the heart in the case herewith reported. These similarities, as well as the differences, were studied to explain the differences in structure of the intrapulmonary arteries in stenosis of the ostium infundibuli of the right ventricle and biventricular origin of the aorta, the condition described herein, and in Eisenmenger complex.

Report of a Case

Clinical Features. The patient, a man, age 47 years, who was a laborer, came to the Mayo Clinic on Jan. 20, 1920, because of hematuria, dysuria and frequency of six weeks' duration. Ten weeks prior to registration at the clinic, transitory pain in the left side of the abdomen, associated with hematuria, dysuria and frequency developed. Twenty years prior to this illness his family physician had told him that he had heart disease. The patient stated that eleven years previously he had had transitory edema of the ankles. This evidently had not recurred.

When the patient registered at the clinic, physical examination revealed evidence of moderate cardiac enlargement. A murmur was heard over the cardiac apex and was associated with a precordial thrill. The legs were moderately edematous, and there was moderate ascites. The blood pressure was 140/80. Cyanosis was not mentioned in the record. Rectal examination revealed a large mass in relation to the prostate. A cystogram showed a filling defect in the outline of the bladder consistent with that caused by a vesical neoplasm. Erythrocytes numbered 2,700,000 per cu. mm. of blood. The patient's general condition was precarious, and he died six days after registration, on Jan. 26, 1920.

Pathologic Features. Necropsy revealed carcinoma of the bladder with extension to the prostate and metastasis to the liver. Of particular interest were the findings in the heart and the intrapulmonary arteries. The heart was moderately enlarged; it weighed 650 Gm. There was a large defect of the membranous portion of the ventricular septum measuring 2.5 cm. in greatest dimension. The aorta which was of normal caliber arose from the right and left ventricles above this defect (fig. 1*A*).

In the right ventricular outflow tract there was a fibrous diaphragm in the center of which there was an opening measuring 1.5 cm. in diameter. This membrane lay at a level above that of the ventricular septal defect and inferior to the pulmonary valve (figs. 1*B* and 2).

In this way the outflow portion of the right ventricle was divided into a substenotic portion and a subvalvular or suprastenotic portion (fig. 1*B*). The distance between the lower portion of the pulmonary valve and the infundibular membrane was 4.0 cm. The orifice of the pulmonary valve which led solely from the right ventricle was of normal caliber or slightly dilated, measuring 7.0 cm. in circumference. The pulmonary valve possessed three normal leaflets.

The wall of the left ventricle was hypertrophied, measuring 1.8 cm. in thickness. The wall of the right

From the Mayo Foundation, Rochester, Minn.

In part an abridgment of a portion of a thesis submitted by Dr. Civin to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Pathology.

ventricle was hypertrophied in its inflow portion and in that part of the outflow tract below the infundibular diaphragm. In these regions it measured from 0.9 to 1.5 cm. in thickness. The outflow portion of the right ventricle above the fibrous diaphragm was noticeably thinner than the wall in the other portion of the right ventricle. The suprastenotic portion of the right ventricular wall measured 0.5 cm. in thickness. The lining of the suprastenotic portion of the right ventricle was irregularly thickened with fibrous tissue.

terioles were considered to be within the limits of normal (fig. 3*A*).

Were it not for the stenosis of the ostium infundibuli the anomalies in this case would fulfill the criteria for a diagnosis of Eisenmenger complex. The stenosis below the pulmonary valve was localized and seemed to be of such degree as to allow adequate flow of blood in the pulmonary system. This categorically removed

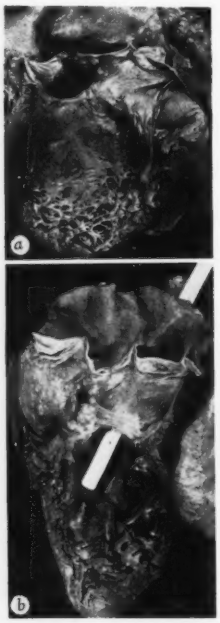

FIG. 2. The suprastenotic portion of the right ventricular outflow tract viewed from above. The pulmonary valve (one leaflet containing an artefact) has a wide orifice. The zone of infundibular stenosis which is unopened lies inferior to the valve.

FIG. 1*A*. The left ventricle. Above a membranous ventricular septal defect the aorta arises in part from each ventricle.

B. The right ventricular outflow tract. Below the pulmonary valve is the opened fibrous membrane which created subpulmonary (infundibular) stenosis. The probe extends from the right ventricle into the aorta. Below the level of the stenosis of the ostium infundibuli the right ventricular wall is hypertrophied.

The mitral, tricuspid and aortic valves and the coronary arteries were normal. The ductus arteriosus was closed.

Grossly the lungs exhibited moderate degrees of congestion and edema. Scattered small metastatic lesions from the carcinoma of the bladder were present in the peripheral portions and involved the adjacent visceral pleura. The major pulmonary arteries showed no gross abnormalities.

On microscopic examination of the lungs the gross findings were confirmed. It is of special interest that structurally the intrapulmonary arteries and ar-

the condition from designation as tetralogy of Fallot.

The case is an example of another condition variously called "stenosis of the infundibulum," "stenosis of the lower bulbar orifice of the infundibulum" or "stenosis of ostium infundibuli." The condition is characterized by a fibrous or fibromuscular localized stenosis of the outflow tract of the right ventricle.[1, 2, 3] In certain cases this condition may be associated

with a closed ventricular septum and origin of the aorta entirely from the left ventricle.[4, 5] In other cases conditions are like the one which we have described in that a ventricular septal defect and biventricular origin of the aorta are associated.[6] The stenosis of the outflow tract in the case presented herein was associated with hypertrophy of the wall of the right ventricle below the stenosis. Above the stenosis the thickness of the wall of the right ventricle was within limits of normalcy. This suggests that while the pressure in the lower part of the right ventricle, that which communicated with the aorta, was elevated, the pressure above the stenotic membrane was of lesser magnitude. The presence of normal intrapulmonary arteries suggests that these vessels were protected by the presence of a stenotic membrane in the outflow tract of the right ventricle.

In order to support the opinion that the stenosis was beneficial to this patient who had biventricular origin of the aorta and so might be simulated surgically in the Eisenmenger complex, the following consideration of the anatomic and functional nature of the Eisenmenger complex is presented.

Anatomic and Functional Nature of the Eisenmenger Complex

The Eisenmenger complex is characterized by the biventricular origin of the aorta above a membranous ventricular defect, or origin of the aorta entirely from the right ventricle, normal or dilated pulmonary arterial channel and hypertrophy of the right ventricle.[7] Because the aorta arises partly or entirely from the right ventricle, there is the possibility of considerable pulmonary blood flow in association with deficient systemic blood flow.[8] Such an effect may in fact exist in those patients with the Eisenmenger complex who die at an early age. In patients who survive infancy, however, the evidence suggests that in spite of the gross vascular derangements, blood flow in the pulmonary system is only a little if at all excessive.[9] In 5 cases of the Eisenmenger complex, Bing, Vandam and Gray[10] found that the volume of blood in the pulmonary capillaries was normal or nearly normal. This finding coupled with the presence of pulmonary hypertension led these investigators to conclude that in the Eisenmenger complex resistance to blood flow through the pulmonary vascular bed must be increased. These investigators also suggested that anatomic lesions of the pulmonary arterioles might exist to explain the results obtained in functional studies and stated that in preliminary pathologic studies this deduction seemed to be supported. Lagerlöf and associates[11] also found pulmonary hypertension in the Eisenmenger complex and interpreted it as resulting from increased resistance to pulmonary flow.

The literature contains little on the microscopic appearance of the intrapulmonary vessels in the Eisenmenger complex. Stewart and Crawford[12] in 1933 reported the case of a man 60 years old who had this malformation. They observed pulmonary vascular changes which they attributed to syphilitic infection. Though the changes in the larger pulmonary arteries may be the result of an infectious process, the appearance of the smaller arteries as illustrated (fig. 3*B*) shows changes in structures which may be interpreted as being due to other circumstances.

In a case of Eisenmenger complex affecting a boy 11 years old, Old and Russell[13] found medial hypertrophy and intimal fibrosis of the small intrapulmonary arteries resulting in severe luminal narrowing. There were also acute inflammatory arterial changes but the latter are conceivably not related to the Eisenmenger complex.

We studied the pulmonary vessels in the case of Eisenmenger complex of a boy, 11 months old, reported by Dry and associates.[14] The small intrapulmonary arteries were characterized by thick muscular medias, thick collagenous adventitias and narrow lumina (fig. 3*C* to *G*). Unlike the observations made on older individuals by Stewart and Crawford[12] and Old and Russell,[13] our young patient had no intimal fibrosis. The intrapulmonary arteries were considered abnormal for a child 11 months old (fig. 2*D*). These vessels, however, were like those in the lungs of normal fetuses and of infants dying in the first half year of postnatal life from causes other than cardiovascular disease.

The changes in the intrapulmonary arteries

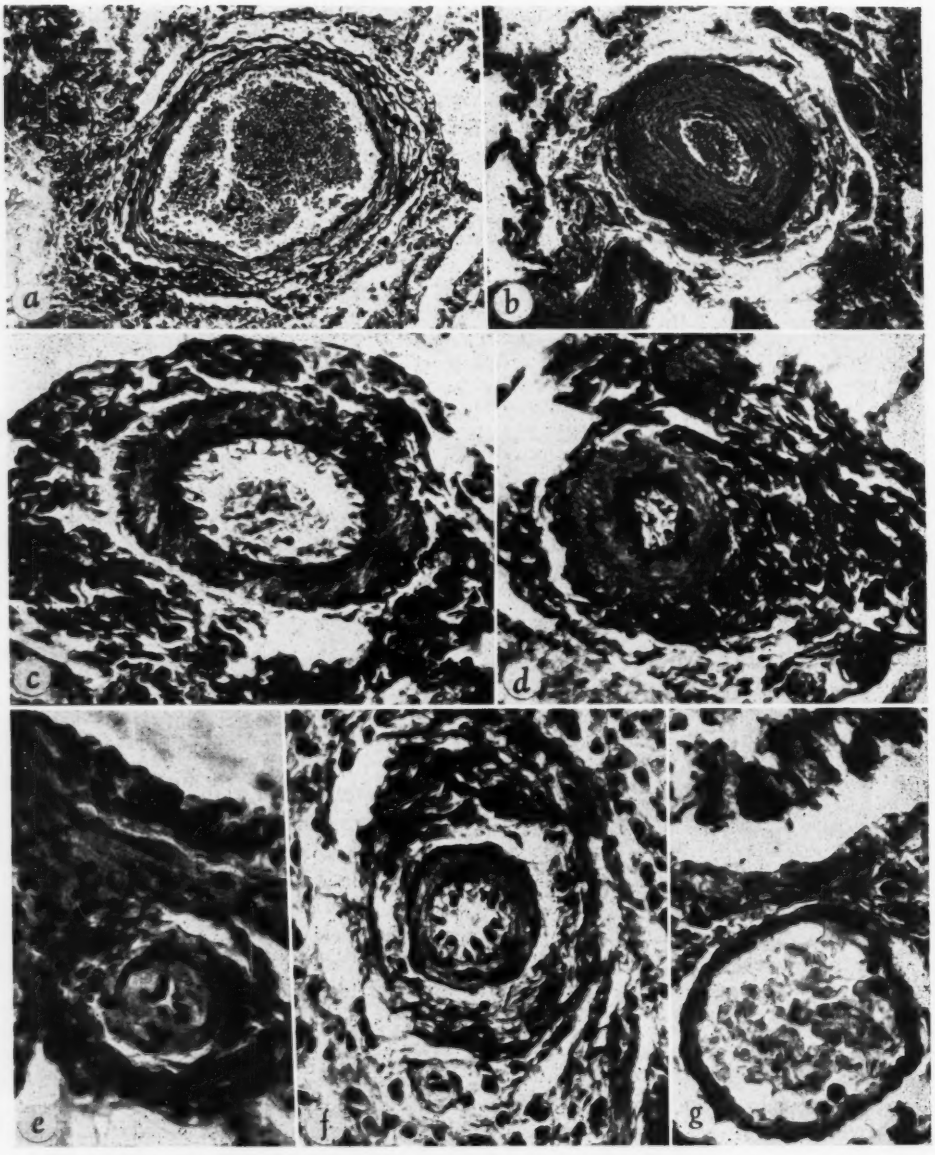

FIG. 3. Intrapulmonary arteries. *A*. A small intrapulmonary artery in the case of stenosis of ostium infundibuli presented. The artery is essentially normal. Contrast it with figure 3*B*. (Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain, ×130.)

B. A small intrapulmonary artery in the case of Eisenmenger complex reported by Stewart and Crawford.[12] There is great thickening of the wall associated with luminal narrowing, (×130). (Reproduced with permission of the authors and the American Journal of Pathology.)

C. Normal pulmonary muscular artery from an infant 6 months old. Though at this stage of development the media is still relatively thick, the lumen is wide. Contrast with the picture in the Eisenmenger complex in *D*. (Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain, ×300.)

D. An intrapulmonary muscular artery in a case of Eisenmenger complex; patient was 11 months

In the case of Stewart and Crawford[12] and the noninflammatory changes in that of Old and Russell[13] are similar to those observed at the clinic in the smaller pulmonary arteries in cases in which aortic coarctation lies proximal to a patent ductus arteriosus.[15] In the latter anomalous complex and in the Eisenmenger complex the function of the right ventricle is similar in that this ventricle supplies blood simultaneously to the pulmonary and systemic systems. Moreover, in this respect the function of the right ventricle is like that in the fetus as the blood ejected from this chamber flows partly to the lungs and partly through the ductus arteriosus into the aorta.[16, 17] We assume that in the normal fetus the distribution of blood from the right ventricle to the lungs on one hand, and to the systemic circulation on the other, is dependent in a measure at least on the state of the smaller pulmonary arterial vessels; that at the level of these vessels the resistance to flow is essentially like that in the systemic circulation. Were resistance to blood flow in the pulmonary vessels lower than resistance to flow in the systemic vessels, as is the normal adult condition, blood from the right ventricle would to a large measure, or completely, be distributed to the lungs. Little or no blood would flow through the ductus arteriosus into the aorta.

On the basis of existing evidence, we are of the opinion that the pulmonary vascular bed of patients with the Eisenmenger complex who survive infancy and who have reasonably well-functioning cardiovascular systems for a number of years, maintains its fetal function; that is, the resistance to flow through the pulmonary vascular bed continues equal to or nearly equal to the resistance to flow in systemic vessels. A similar interpretation of the postnatal functioning of the pulmonary vascular bed was expressed as likely in cases in which aortic coarctation lies proximal to a patent ductus arteriosus.[15] The medial hypertrophy of the smaller pulmonary arteries in association with coarctation of the aorta proximal to the patent ductus arteriosus and with the Eisenmenger complex, is interpreted as reflecting increased resistance to pulmonary blood flow. The medial hypertrophy also is interpreted as representing maintenance of a fetal type of pulmonary artery.

This anatomic state of the pulmonary vessels, in our opinion, need not be considered as representing an anomaly. On the contrary we consider it a part of a compensatory mechanism which permits the patient to remain alive. The individual with such a compensatory mechanism pays a price, however, since the mechanism as outlined has pulmonary hypertension as a component part. The intimal fibrous changes which may be present in the pulmonary vessels of older patients who have Eisenmenger complex cause further narrowing of the vessels. These seem to arise after medial changes are evident and are considered to be a reaction to the traumatic influence of existing pulmonary hypertension. Whereas the medial hypertrophic changes are associated with luminal narrowing of desirable and perhaps changing degree,[8, 10] the intimal changes cause further and fixed narrowing of the lumen. The narrowing so caused may be of such degree as to increase the resistance to pulmonary blood flow above that to systemic flow. Such a development would cause a greater distribution of the right ventric-

of age. In contrast with the normal, *C*, the thick media is associated with a narrow lumen. (Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain, ×300.)

E. Small intrapulmonary artery in a case of Eisenmenger complex; child was 11 months of age. The media is thick and the lumen is narrow. The picture is like that in the normal newborn (see *F*) and in contrast to the picture at a later stage in development (*G*). (Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain, ×450.)

F. A normal small intrapulmonary muscular artery of an infant 4 days old. The media is thick and the lumen narrow. (Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain, ×450.)

G. A normal small intrapulmonary muscular artery of an infant 6 months of age. The picture is different from that in the newborn period (*F*) and from that in the Eisenmenger complex, (*E*). The media has become thin and the lumen wide. (Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain, ×450.)

ular blood to the aorta and a concomitant lessening in the volume of pulmonary blood flow.

It seems reasonable to speculate that the characteristic late appearance of cyanosis in cases of the Eisenmenger complex may be the result of such intimal changes. When the intimal changes develop in association with the Eisenmenger complex, the condition present is functionally comparable to that in tetralogy of Fallot. The intimal changes being in the smaller pulmonary arteries are, however, beyond reach of a by-passing operation as practiced in the tetralogy of Fallot. It is evident from the foregoing that in the patient who has an Eisenmenger complex, the responsibility of regulating pulmonary and systemic blood flow seems to fall in part on the smaller pulmonary arterial vessels and that eventually this function causes irreparable changes in these. It would be desirable if in the Eisenmenger complex responsibility for regulating the distribution of right ventricular blood were removed from the intrapulmonary vessels in order to protect these from developing occlusive intimal changes.

Comment

The case of infundibular stenosis herein presented suggests a method for shifting the responsibility away from the vulnerable intrapulmonary vessels. It will be recalled that the heart in the case reported showed certain features of the Eisenmenger complex, namely the biventricular origin of the aorta above a ventricular septal defect, right ventricular hypertrophy, and absence of stenosis of the pulmonary valve or pulmonary trunk. There was one additional feature of importance in the form of localized stenosis of the outflow tract of the right ventricle at a level above that of the ventricular septal defect. Thus the right ventricle being in communication with the aorta undoubtedly maintained a high level of pressure but the pulmonary vessels and, presumably, the pulmonary blood pressure were normal. This interpretation gains some support from a case (case 2) recently reported by Dow and associates[18] and by a patient studied at the Mayo Clinic by Drs. Willius, Dry and Wood. In Dow's case studies by cardiac catheterization revealed the pulmonary arterial pressure to be 33 mm. of mercury systolic and 14 diastolic. In the outflow portion of the right ventricle the pressures were 33 mm. systolic and 1 mm. diastolic, whereas in the main portion of the right ventricle the systolic pressure was 99 mm. Hg and the diastolic 1 mm. These findings suggested to the authors that there was stenosis of the ostium infundibuli rather than in the infundibulum itself or in the pulmonary valve.

Drs. Willius, Dry and Wood of the clinic studied in March, 1950, a patient 19 years old. Cardiac catheterization studies indicated that the malformation was like that in the case we have reported. In their patient, the systolic blood pressure in the right pulmonary artery and in the pulmonary trunk was 12 mm. of mercury and the diastolic pressure 3 mm. of mercury. In the outflow tract of the right ventricle, the pressure was 36 mm. systolic and 2 mm. diastolic. In the inflow part of the right ventricle, a systolic pressure of 118 mm. was recorded and the diastolic pressure was 3 mm. The catheter passsed from the right ventricle into the aorta and into the innominate artery. In the latter vessel the systolic pressure was 112 mm. of mercury and the diastolic, 83 mm. The blood in the right atrium was 77.7 per cent saturated with oxygen, that in the right ventricle 75 per cent saturated, and that in the innominate artery 92.5 per cent saturated.

We interpret the circumstance of the infundibular stenosis in our case as follows: The stenosis of the outflow tract was of such proportion as to create sufficient resistance for the right ventricle to supply blood to the aorta but at the same time wide enough to allow an adequate flow of blood to the lungs without stress on the intrapulmonary arteries. The stenosing membrane seems to have been responsible for a balanced circulation and at the same time a protection of the smaller pulmonary arteries.

The suggestion stimulated by the case presented is that in the Eisenmenger complex the eventual appearance of detrimental intimal changes in the intrapulmonary arteries can possibly be prevented and adequate pulmonary

blood flow maintained by surgical creation of an appropriate degree of stenosis of the right ventricular outflow tract or pulmonary trunk (fig. 4).

Such a procedure must be considered for the future. Experimental attempts at creating subpulmonary or pulmonary stenosis must first prove successful. Moreover, sufficient studies must be made on patients with the Eisenmenger complex to indicate what degree of pulmonary stenosis would be ideal in protecting the pulmonary vessels and at the same time in allowing adequate flow of blood to the lungs.

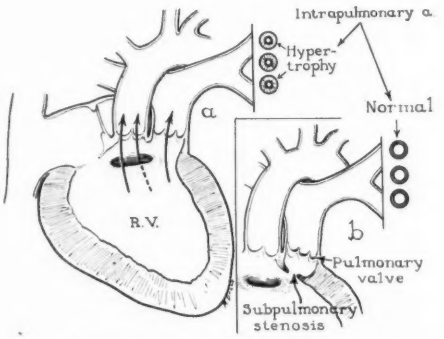

FIG. 4. Representation of the structural changes in the Eisenmenger complex, *a*, and in the case reported, *b*. In the Eisenmenger complex the intrapulmonary arteries show thickening of the walls and narrow lumina. In the case of stenosis of ostium infundibuli, *b*, the subpulmonary stenosis of the right ventricle seems to have spared the intrapulmonary arteries from organic changes.

SUMMARY

In the case of a 47 year old laborer with a normal pulmonary artery, ventricular septal defect, biventricular origin of the aorta and subpulmonary (infundibular) stenosis of the outflow tract of the right ventricle, the intrapulmonary arteries and arterioles were normal.

In the Eisenmenger complex the intrapulmonary arteries are characterized by medial hypertrophy and, ultimately, intimal fibrosis. The stenosing membrane in the right ventricular outflow tract of the case presented herewith seems to have prevented the formation of organic changes in the intrapulmonary arteries.

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Hemodynamic Study of a Case of Anomalous Pulmonary Venous Drainage

By W. Hwang, M.D., O. Prec, M.D., K. Kuramoto, M.D., S. Segall, M.D. and L. N. Katz, M.D.

Complete drainage of the pulmonary veins into the right heart is one of the rarest and most severe congenital cardiac anomalies. The X-ray studies may suggest this diagnosis if pulmonary veins enter either coronary sinus or inferior vena cava. In the case reported, right heart catheterization and angiocardiography were used and the diagnosis of persisent left superior vena cava and partial direct drainage of the pulmonary veins into right auricle was made.

UNTIL RECENTLY our knowledge of anomalous drainage of pulmonary veins into the right heart has been drawn mainly from postmortem examinations. Among some hundred reported cases, complete drainage of the pulmonary venous blood into the right auricle or its tributaries occurred in about 35 per cent. Eight patients with such complete anomalous drainage lived for 6 months. Since it is imperative to differentiate this condition clinically from other types of cyanotic congenital heart disease which are amenable to existing surgical treatment, additional information on the diagnosis of such anomalies during life is of practical importance as well as of academic interest.

The following is a case of nearly complete pulmonary venous drainage into the left superior vena cava and right auricle diagnosed with the aid of right heart catheterization and angiocardiography.

Case Report

A 31 month old white boy, known to have congenital heart disease, was admitted for investigation in order to arrive at a more definitive diagnosis. The child had a normal birth. Shortly afterwards, a heart murmur was noted. He was cyanotic from early infancy, especially after excitement or exertion. The cyanosis had been gradually increasing in intensity. Squatting was frequent. In the three-month period prior to admission, the parents noticed that the boy's physical activity had become markedly limited and cyanosis had increased. He had had chicken pox and bronchitis at the age of 18 months. There was no history of convulsive seizures. The family history was essentially negative.

On admission he was found to be fairly well developed. Mentally he was quite alert, although he could only speak a few simple words. There was marked cyanosis of the lips and finger beds. No clubbing of the fingers or toes was present. The chest was not deformed. The lungs were clear. The heart was not enlarged to percussion; there was no precordial thrill. The second pulmonic was louder than the second aortic sound, although there was no accentuation of either. A harsh blowing systolic murmur was heard over the whole precordium with maximal intensity in the third intercostal space to the left of the sternum. Blood pressure was 118/80 and equal in both arms. Pulse rate was 88 per minute. Abdominal organs were essentially normal to palpation. There was no evidence of congestive heart failure.

Laboratory findings: The red blood cell count was 6.22 million per cu. mm. with 14.0 Gm. per cent of hemoglobin (calculated from oxygen capacity of blood). Urinalysis was normal.

Fluoroscopically, the lungs were clear; there were no abnormal parenchymal markings. The silhouette of the heart and great vessels was notable only in that there was a prominent, well-defined bulge directly below the aortic knob in the posteroanterior view (fig. 1). In the partial left anterior oblique position, continuous with this prominence and extending upward, was a paramediastinal shadow which was considered at that time to be a branch of the pulmonary artery. The hilar shadows were not remarkable. The pulsation of the pulmonary arteries were rather small.

The electrocardiogram showed abnormally tall R waves in aV_R and in leads over the right precor-

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dium; the QRS configuration of aV_F was analogous to that of the right precordial leads. These findings were interpreted as right heart strain in an electrically vertical heart.

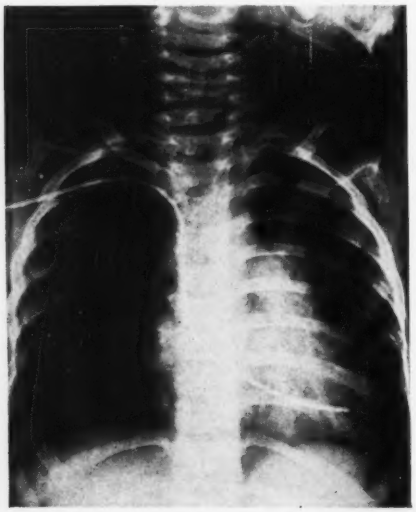

FIG. 1. Anteroposterior roentgenogram of chest showing an abnormal left upper paramediastinal shadow interpreted as persistent left superior vena cava. The catheter is in the right ventricle.

TABLE 1.—*Results of Right Heart Catheterization*

Catheter Location	O_2 Content (Vol.%)	Pressure (mm. Hg)
Right ventricle	15.6*	108/5
Right auricle	15.5†	9-1
Anomalous Pulmonary Vein	17.1	12-5
Superior vena cava	11.2	
Inferior vena cava	8.1	

Arterial oxygen content: 16.6 vol. %
Arterial oxygen capacity: 18.5 vol. %
Cardiac output‡:
Systemic flow: 0.94 liters/min.
Pulmonary flow: 5.3 liters/min.
Distribution of pulmonary flow:
To the right heart: 4.6 liters/min.
To the left auricle: 0.7 liters/min.
Interauricular right to left shunt: 0.24 liters /min.

* Average of three blood samples from the chamber.

† Average of two blood samples from the chamber.

‡ The oxygen consumption is assumed to be 80 cc./min. as the patient was not sufficiently cooperative to give a consistent oxygen consumption test.

Right heart catheterization was done under light anesthesia with rectal pentobarbital, and the data obtained are presented in table 1. During the procedure, as the catheter was being manipulated in the right atrium, the tip projected beyond the right border of the heart shadow (fig. 2). Analysis of the oxygen content of a blood sample taken at this point, indicated that the catheter had entered a pulmonary vein which drained directly into the right atrium. The catheter was withdrawn from the anomalous vessel and introduced into the right ventricle, but attempts to insert the catheter in the pulmonary artery were finally abandoned because of the irritability of the heart, which led to frequent premature ventricular systoles.

Analysis of the results showed: (1) Blood samples taken at two separate points in the superior vena cava had a high oxygen content (11.2 volumes per cent) as compared to that in the inferior vena cava (8.1 volumes per cent). This indicated an admixture of oxygenated blood in the superior vena cava prior to its entrance into the right atrium. In view of this fact and the abnormal shadow at the left upper paramediastinal region in the chest film (fig. 1), this strongly suggested the presence of a persistent left superior vena cava draining the left lung and eventually emptying into the right auricle via the right superior vena cava.

FIG. 2. Anteroposterior roentgenogram of chest showing that the catheter has entered an anomalous pulmonary vein which drains directly into the right atrium.

(2) Direct drainage from at least one pulmonary vein from the right lung into the right atrium was demonstrated by the insertion of the catheter in the anomalous vessel.

(3) The relatively small difference between the oxygen contents of the arterial blood and that of the right ventricle indicated that nearly all the pul

monary drainage was into the right atrium. The oxygen contents indicate that about seven-eighths of the pulmonary venous blood drained into the right heart and one-eighth into the left auricle.

(4) Pulmonary stenosis, though not directly demonstrated by an increased pressure gradient across the orifice, was inferred from the small pulmonary arterial pulsation despite the high right ventricular systolic pressure and the high pulmonary blood flow.

(5) An interauricular septal defect was necessarily postulated as the path is essential for the maintenance of systemic flow.

Angiocardiography was done to demonstrate the presence of an interauricular septal defect and any associated anomalies in the cardiovascular system. Thirty-five cubic centimeters of 70 per cent Diodrast was injected. Figure 3 shows clearly the interauricular communication. The pulmonary arteries were found to be unusually wide and tortuous. No definite area of stenosis could be identified, partly due to an overlapping of several structures at the point where the stenosis should be expected.

FIG. 3. Left anterior oblique roentgenogram of chest taken after intravenous injection of Diodrast. The interauricular communication is demonstrated by the streaming of dye from the right directly into the left atrium.

DISCUSSION

The embryonic development of anomalous pulmonary veins has been adequately reviewed and discussed by MacManus,[13] Brody[3] and Brantigan.[2] It is generally contended that anomalous pulmonary veins causing partial shunt of blood into the right heart may not give rise to any symptoms or signs, and are compatible with a normal life. Their presence occasionally give rise to grave consequence when the contralateral lung with normal drainage is therapeutically obliterated (thoracoplasty, lobectomy, pneumonectomy) for some underlying pulmonary disease. It is conceivable that some of the immediate accidents following pneumothorax or other collapse therapy may be due to such anomalous drainage of the lung. On the other hand, the prognosis is very grave[3,14] when more than 50 per cent of the pulmonary blood is shunted back to the right side of the heart. When the drainage of the lungs into the right atrium is complete, with few exceptions, patients die early, either because of insufficient systemic supply or right ventricular failure. The hemodynamics involved in this anomaly merit further comment.

When all the pulmonary venous blood is returned to the right atrium, the only pathways through which the systemic circulation can be supplied would be one or more intracardiac shunts. In Brody's analysis of 105 autopsies with anomalous drainage of the lung to the right heart, 38 cases had total aberrant drainage. Aside from 5 cases of cor biloculare, which do not strictly belong to this group, a patent foramen ovale, when this defect was looked for, was found in all cases. Only 4 had an interventricular septal defect, and 10 had a patent ductus arteriosus. Obviously, by far the most important shunt in this condition is the interauricular septal defect. When interauricular septal defects exist alone or in association with other congenital heart defects the direction of the shunt is almost always from left to right.[1,7,10,16] This has been explained on the basis of the relative positions of the auricles[15] and the greater distensibility of the right auricle.[12] In cases of complete or nearly complete drainage of the pulmonary blood into the right atrium, on the contrary, the return flow to the right auricle is so much greater than that to the left side (7 times greater in the present case) that the pressure gradient between the auricles is reduced and the shunt becomes right to left. Furthermore the pulmonary stenosis that is considered to have been demonstrated in this case elevated the end diastolic pressure in the

right ventricle. This further facilitated the shunting of blood from right to left.

The prognosis of this patient is, of course, very grave. Brody's analysis showed that in spite of its vital role the foramen ovale gradually closed in all cases. Moreover the strain on the right heart, produced both by the high volume flow and the pulmonary stenosis, must be great. The increased cyanosis in the past 3 months and the abnormally low (about 8.0 volumes per cent) systemic venous oxygen content indicates that either the interauricular communication is closing or physical activity has increased out of proportion to that which can be maintained by the amount of blood coming from the lung and that passing through the interauricular septal defect. The electrocardiogram, as presented above, confirmed the presence of right ventricular strain. A downhill course leading to early death seems inevitable, if no drastic procedure is done to correct the anomaly. Brantigan mentioned[2] the possibility of a surgical anastomosis between the anomalous pulmonary vein and the left auricle in such cases. The production of such an anatomic correction indeed seems worth attempting as it may offer the only hope for these patients. If the anatomic structure does not lend itself to this type of correction, enlargement of the interauricular septal defect may increase the amount of systemic blood supply resulting in a physiologic correction.

A definite diagnosis of complete or partial drainage of pulmonary veins into the right heart during life was made possible only after the utilization of right heart catheterization and angiocardiography. To date 10 cases have been reported in which the diagnosis was made with one or both of these technics. Dotter and his associates reported two cases of partial drainage of the pulmonary veins into the inferior vena cava[3]; both were diagnosed with the aid of angiocardiography and one was confirmed by right heart catheterization. Grishman and associates[9] recently reported three similar cases diagnosed by chest x-ray and angiocardiography. Both groups of authors emphasized the diagnostic significance of the laterally convex falciform shadow in the ordinary posteroanterior chest film. In fact, the studies of all 5 reported cases were initiated because of the presence of such abnormal shadows in the lower lung fields. Bruce and his associates[4] made the diagnosis in their two cases by direct catheterization of the anomalous veins. One of their diagnoses was later confirmed by operation and autopsy. Johnson and McRae[11] demonstrated by catheterization what was probably an anomalous right pulmonary vein, although the possibility of the catheter having entered a hemangioma could not be completely ruled out. Cournand's[6] and Chapman's[5] series of catheterized cases both included one case each of such anomalous pulmonary vein.

Grishman and co-workers remarked that vascular structures have to be of a certain size and density before becoming roentgenologically demonstrable. In the case presented, the anomalous vessels were not demonstrated either in the ordinary x-ray films or by angiocardicgraphy. But even when the latter method is successful in demonstrating one or more such vessels, the information is inadequate. Right heart catheterization, we believe, is essential in such cases. Beside confirming the diagnosis, a comparison of oxygen contents of blood from the great vessels, chambers of the heart and peripheral artery help to quantitate the amount of anomalous drainage. This approximate quantitation, as demonstrated in our case, is obviously more important in determining the prognosis and management of the patient than the mere demonstration of the presence of such an anomaly.

Summary

1. A case of nearly complete anomalous drainage of pulmonary veins into the right atrium and persistent left superior vena cava with associated interauricular septal defect and pulmonary stenosis diagnosed by right heart catheterization and angiocardiography is reported.

2. The hemodynamics in this anomaly, the prognosis and possible management of this patient are discussed.

3. The relative merits of catheterization and angiocardiography as diagnostic procedures for this condition are presented.

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Survival to the Age of Seventy-Five Years with Congenital Pulmonary Stenosis and Patent Foramen Ovale

By PAUL D. WHITE, M.D., JOHN W. HURST, M.D., AND ROBERT H. FENNELL, M.D.

It is very rare for a person with cyanosis and finger clubbing due to congenital heart disease to reach old age. Survival beyond the age of 50 has been noted only a few times and, as far as we are aware, survival of a person with morbus caeruleus beyond 70 years is unique. The patient reported below showed at autopsy marked pulmonary stenosis and patency of the atrial septum simulating the tetralogy of Fallot. One of the reasons for the long survival was undoubtedly a markedly developed collateral bronchial circulation.

THE SYNDROME of pulmonary stenosis with patency of the foramen ovale is a distinct entity though readily confused clinically with the tetralogy of Fallot. The oldest previously recorded case proved at autopsy was 57 years old.[5] It is therefore of particular interest to report herewith the case of a woman with this congenital anomaly who not only survived to the age of 75 years but who also lived a useful and comfortable life despite considerable cyanosis until death from cardiac and cerebral vascular failure.

Pulmonary stenosis with patency of the foramen ovale was one of the first congenital anomalies to be recognized. Morgagni described a girl aged 16 years with this condition in 1761. Six more cases were reported during the next 100 years.[2–8] We have recorded chronologically in the bibliography[9–32] 31 more instances since Wilk's paper[8] of 1859. Bertin and Breschet's case, quoted by Gintrac[5] and Lallemand,[6] the oldest previously recorded, has been referred to several times as though it were new each time. Among 37 of this group of 38 cases the ratio as to sexes was 16 males to 21 females and the ages at death were in the first decade in 9 cases, in the second in 16, in the third in 8, in the fourth in 2, in the fifth in 1, and in the sixth in 1. Our case died in the eighth decade.

We would like to emphasize that pure pulmonary stenosis, pulmonary stenosis with patency of the foramen ovale, and pulmonary stenosis with ventricular septal defect and dextroposition of the aorta (tetralogy of Fallot) are three distinct clinical entities with different clinical and laboratory findings. In addition, the prognosis is not the same for all three and the surgical approach in the three conditions also differs. It is, therefore, important to differentiate and to report all three syndromes as separate conditions and no longer to group them under general "pulmonary stenosis."

The clinical features of this syndrome have recently been reviewed by Selzer and his associates[30]: Cyanosis, clubbing of the fingers, polycythemia, loud systolic murmur at the pulmonary area, right ventricular hypertrophy, prominent P waves in the electrocardiogram, enlarged x-ray shadow of the pulmonary artery with moderate-sized hilar shadow. These findings differ from the tetralogy of Fallot with respect in particular to the x-ray evidence; the typical x-ray heart and vascular shadow in the tetralogy of Fallot shows a small pulmonary artery and small hilus shadows. It differs from pulmonary stenosis with closed septa with respect to the clinical findings of cyanosis, clubbing, and polycythemia, which are absent in the latter except for terminal cyanosis when heart failure develops.

CASE REPORT

M. T. M., born May 29, 1874, was first examined by one of us (P. D. W.) on April 24, 1922. At that time (at the age of 48) she gave the following history.

Heart disease had been known since early childhood but the patient did not think that she had been blue at birth. Cyanosis gradually developed in her early youth and was present in considerable degree later. Shortness of breath was an early symptom and limited her activity in playing with

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other children. Her heavy breathing always revealed her hiding place to the others in their game of hide and seek. This shortness of breath on effort continued to be a constant symptom throughout her life. She had recently had her teeth extracted, two at a time, without complications.

Her general health had always been rather frail, and she had had pneumonia at the age of 18, typhoid fever at 19, severe "jaundice" at 21, and influenza at 33. The last named illness was followed by marked "nervous exhaustion." At that time, 1907, because of fear of heart failure she was digitalized for the first time and had continued to take digitalis ever since. There had been no chest pain, hemoptysis, or ankle edema.

She had worked steadily for many years as a librarian and secretary. For six years (1912–1918) she had assisted in the record room at the Peter Bent Brigham Hospital. While there she was at one time examined by Dr. Maude Abbott who diagnosed deviation of the aorta and possible pulmonary stenosis.

Family history revealed that she was an only child. Her father died at the age of 75. Her mother was 76 years old at this time (in 1922) and in good health; she lived to be 88 years old.

Physical examination showed a rather short, otherwise well developed and nourished middle-aged woman of 48, alert, breathing normally with moderate cyanosis of the face, lips, tongue, and finger tips. There was doubtful clubbing of the fingers. The pulse was regular at 80. The blood pressure was 110/85. There was no precordial thrill palpable. The cardiac apex impulse was faint in the fifth intercostal space, 0.5 cm. outside the left midclavicular line. The first sound was fairly loud at the apex, but the second sound was diminished throughout. There was a loud blowing systolic murmur heard all over the precordium, loudest in the second left intercostal space near the sternum. There were no diastolic murmurs. The lungs, abdomen and the remainder of the physical examination were negative. There was no edema of the extremities.

For the electrocardiogram see figure 1*A*.

A diagnosis was made of congenital pulmonary stenosis without heart failure. Since there was no evidence of congestive failure, digitalis was discontinued.

The next examination was on September 26, 1931. She had been quite well during the intervening nine and one-half years, still working as a librarian and secretary, and although she was bothered by shortness of breath and occasional palpitation, her health was fairly good.

Physical examination revealed that the heart had increased slightly in size. The murmur in the pulmonary area was of about grade 4 intensity and on this examination, a slight systolic thrill could be felt in the pulmonary area. The cyanosis of the face and finger tips was still evident and on this examination slight clubbing of the fingers was definitely noted.

Laboratory Data (Sept. 26, 1931): The red blood count was 6,750,000. The hemoglobin was 90 per cent (Sahli). The white blood count was 7,850.

Fluoroscopic examination showed slight to moderate cardiac enlargement. The transverse diameter of the heart was 13.4 cm. and the internal diameter of the chest was 22.1 cm. The distance across the great vessels at the base of the heart was 6.5 cm. The hilar vascular shadows were well seen.

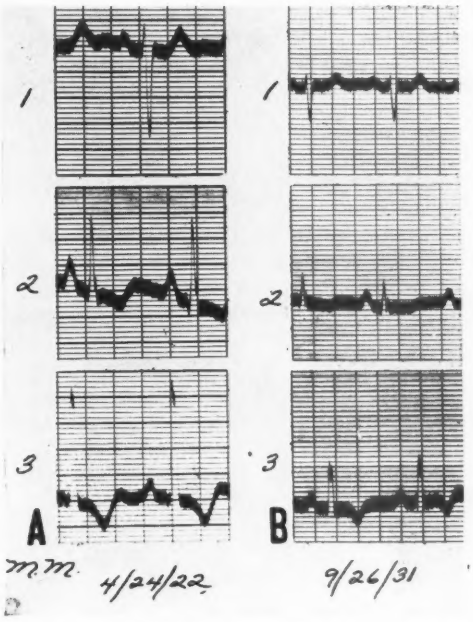

FIG. 1. *A*. 4/24/22. Electrocardiogram showing a rate of 80, marked right axis deviation, prominent P waves, and inverted T_2 and T_3. *B*. 9/26/31. Electrocardiogram showing a rate of 75, marked right axis deviation, diphasic T_2 and inverted T_3. The voltage is less than on 4/24/22.

For the electrocardiogram see figure 1*B*.

In 1931 an adult cyanotic patient with the findings as listed above was considered to have the tetralogy of Fallot, and therefore this diagnosis was made on this examination.

She continued to be fairly well from 1931 until 1949. The physical examination changed very little except that the cyanosis and finger clubbing increased gradually through the years.

On March 19, 1949, she was seen by Dr. Charles Walcott of Cambridge, Massachusetts, because of her complaints of increasing dyspnea and edema of the legs. Right heart failure was diagnosed and

digitalis, low-sodium diet, and rest were prescribed. After a few days she improved.

From April 3, 1949, until May 7, 1949, she had several episodes of dyspnea and syncope. During this period the pulmonic systolic murmur decreased greatly in intensity.

On May 6, 1949, she had a paroxysm of auricular fibrillation with a ventricular rate of 96 for which 0.2 Gm. of quinidine sulfate were given. The paroxysm stopped within 20 minutes. The syncopal attacks continued until she died suddenly at 12 noon on May 7, 1949. The cause of death was considered to be heart failure associated with cerebral ischemia and possibly cardiac arrhythmia.

Autopsy. The autopsy was performed eight hours after death by one of us (R. H. F.).

FIG. 2. A view of the greatly stenosed pulmonary orifice looking down from above.

The body was that of an elderly woman measuring 150 cm. in length and weighing an estimated 130 pounds. The entire body was cyanotic with marked lividity of the dependent portions. There was minimal clubbing of the fingers. Slight pitting edema of the ankles was present.

The pericardium contained a few cubic centimeters of amber fluid. The heart weighed 390 grams. The right ventricle was almost as large as the left. The right atrium was three times normal size and its wall varied from 2 to 3 mm. in thickness. The left atrium did not appear enlarged. The foramen ovale was patent, the defect measuring 1.2 cm. in greatest diameter. The guard on the left side covered approximately one-third of the defect. At the edges of the opening the endocardium was thickened and gray. On the left side a fibrous cord 1 mm. in diameter extended across the foramen anteroposteriorly and was attached near the edges. The right ventricular wall averaged 12 mm. in thickness, but varied from 18 mm. in the conus to 5 mm. near the apex. The columnae carneae were prominent. The myocardium of the left ventricle was 18 mm. thick near the base but tapered to 10 mm. at the apex. The distance from the atrioventricular valve ring to the apex of the chamber was 5 cm. on the right and 6.5 cm. on the left. The myocardium was red and firm except in the anterior wall of the right ventricle where the wall was thinned and there were prominent gray strands of tissue, especially conspicuous beneath the endocardium. The endocardium of the right ventricle was gray and opaque and this became very marked near the pulmonic ring.

The infundibulum of the right ventricle narrowed gradually as it approached the pulmonic ring. The narrowing was accentuated by the markedly hypertrophied columnae carneae and just proximal to the pulmonic ring for a distance of 5 mm. the maximum diameter of the infundibulum was 8 mm. A true subpulmonic stenosis was thus manifest. The pulmonic ring was 10 mm. in diameter and the artery just distal to the ring was 20 mm. in diameter. Jutting into the lumen of the base of the pulmonary artery was the markedly stenotic pulmonary valve which was a dome-shaped structure and measured 20 mm. in length. At the apex of this structure was the valve orifice which was 3 mm. in diameter (fig. 2). About the rim of the opening were adherent, tiny, grayish-pink vegetations. The valvular structure was tough, fibrous, uniformly smooth, and 1 mm. thick throughout. There were 3 attachments of this structure to the wall of the pulmonary artery equidistantly placed around the circumference of the artery, and these were interpreted as probably representing valve commissures (fig. 2). The right posterior attachment extended to within 4 mm. of the opening, the other two to within 8 mm. Between these attachments were recesses extending down to the valve ring between the wall of the artery and the dome-shaped projection.

The chordae tendineae of the tricuspid valve were slightly thickened. Near the middle of the anterior cusp was an area of calcification 3 mm. in diameter which protruded on the atrial surface. The tricuspid valve ring was 9.5 cm. in circumference, the mitral 8.5 cm., and the aortic 7.5 cm. The latter two valves were normal in appearance.

There was minimal atherosclerosis of the coronary arteries but no evidence of an old or recanalized thrombus was seen.

The aorta was normal in size and position and showed moderate atherosclerosis. The pulmonary artery was 2 cm. in diameter just above the pulmonic valve ring but dilated gradually so that the primary trunk at the bifurcation was 5 cm. in diameter. The dilatation ended abruptly at the bifurcation.

The lungs were well aerated and the pleural

surface was a variegated blue-red. There were numerous fibrous adhesions to the chest wall. The trachea contained a profuse amount of pink, frothy fluid. The bronchial arteries were injected in situ via the aorta after ligation of its main branches. A colored radiopaque plastic solution in acetone was used.*

after each injection and the lungs were finally digested in hydrochloric acid. The bronchial arteries arose from the aorta, both at the arch and from the descending aorta and anastomosed around the hilar region to form a network of vessels which proceeded out to the lung parenchyma, most of them in direct relationship to the bronchi. Some of these vessels

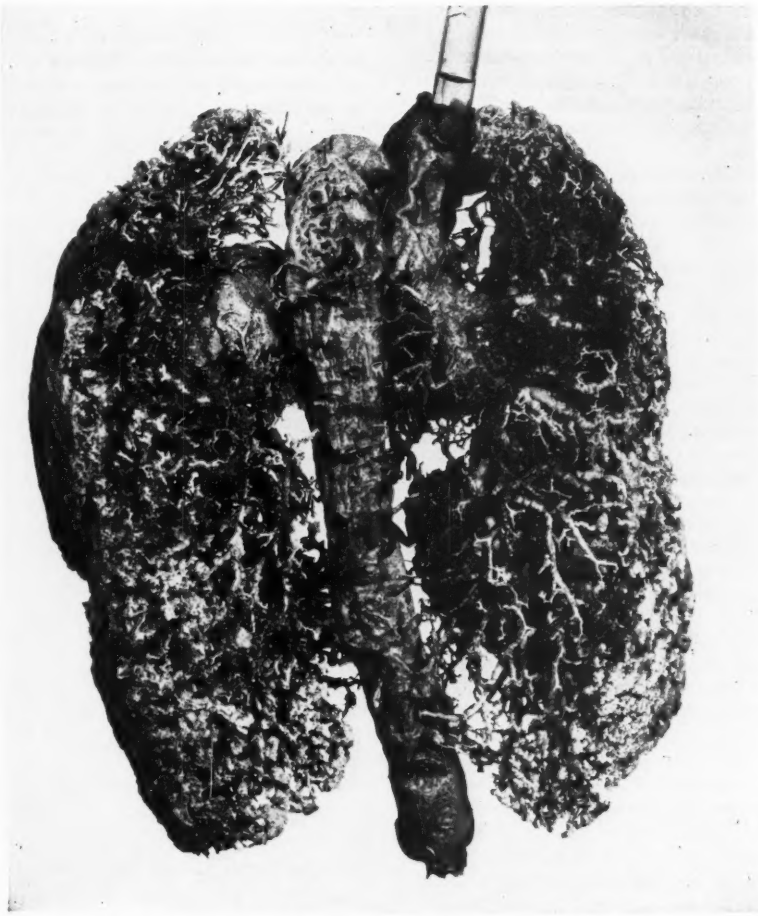

FIG. 3. Photograph of injection of pulmonary arteries and entire bronchial tree. Posterior view of digested cast. Note large number of bronchial arteries entering right lung from descending aorta. Also note the huge pulmonary artery to the left of the aorta exposed by clearing away some of the lung and vessels overlying it.

Later the pulmonary arteries and entire bronchial tree were injected (fig. 3). X-ray films were taken

measured 6 to 8 mm. in diameter. As they coursed along the bronchi, anastomoses with the pulmonary artery were seen in at least 7 places. The continuity of the two circulations was definitely established by the mixing of the two colored injected masses. A bronchial artery 3 mm. in diameter arose from the plexus of esophageal and bronchial vessels and

* The authors wish to express their gratitude to Drs. B. H. Landing and James T. Weston of the Childrens Hospital, Boston, for the injection and examination of the lungs.

passed directly into the pulmonary artery bulb posteriorly. In several areas bronchial vessels left the bronchi to course into lung parenchyma and form a small bulb or plexus of vessels far out in the periphery with no precapillary anastomoses to pulmonary vessels. Small branches of the pulmonary artery continued outside of the lung in the adhesions. In the lower portions of the lung there was a definite, somewhat generalized tubular dilatation of the smaller bronchi and bronchioles.

The liver weighed 850 Gm. and the surface was ragged with fibrous tags. It showed increased resistance but the architecture was normal. The gastrointestinal tract, spleen, pancreas, adrenals and kidneys were not unusual. The left wall of the uterus was partially replaced by soft, reddish-gray, granular tissue but the cervix was not involved. The tubes and ovaries were normal.

Microscopically the myocardium of the right ventricle was extensively replaced by fibrous tissue, the inner half of the wall being most severely damaged. In the thinned area on the anterior wall only scattered muscle fibers remained and the wall consisted almost entirely of dense scar tissue. The muscle fibers that remained varied in size and shape and on cross section the nuclei were bizarre in shape. The vessel walls were thickened, some eccentrically, and primarily by intimal proliferation. Medial thickening and scarring and reduplication of the internal elastic lamina were evident in the arteries. The endocardium was thick throughout the right ventricle but this was especially marked along the anterior wall and about the apex where there were thrombi of varying ages in the crevices between the columnae carneae. The older ones were almost completely organized and consisted of loose connective tissue, and recanalization about the columnae had taken place. In the left ventricle the changes were minimal. Only a few patches of fibrous tissue were seen in the myocardium.

The pulmonic valve was also examined microscopically. It was thickened and consisted of dense collagen with areas of myxomatous degeneration. The vegetations consisted of hyalinized connective tissue with adherent clumps of fibrin. No bacteria were seen. Small calcium deposits were in the valve near the tip. The tricuspid valve also contained myxomatous areas and was thickened.

The lungs showed the large alveoli and the club-shaped ends of ruptured septa characteristic of emphysema. Several areas of fatty replacement suggested healed focal pneumonitis. There were no significant changes in the vessels.

The liver was normal except for increased numbers of round cells in the portal areas. There was no evidence of chronic passive congestion. The kidneys showed mild nephrosclerotic changes. The wall of the uterus was invaded by a well-differentiated adenocarcinoma.

Discussion

The record for longevity established by this case was extraordinary in view of the very high degree of valvular and infundibular pulmonary stenosis associated with a patent foramen ovale. Familial longevity was in her favor, as was the fact that she lived a careful life and was never under very severe strain. Also the evolution of her signs suggested that her pulmonary stenosis may have slowly increased in degree in the course of years. Finally, the compensation received through the bronchial circulation, as found by the injection of the blood vessels of the lungs, was undoubtedly an important factor in her survival.

It is of great interest that she was alert and mentally keen through practically all her life. She was an unusually bright and witty person and even within a few months of her death still showed her mental acuity in conversation. Thus, despite such a handicap, she made herself a useful citizen as well as a long-lived one, much as had Henry Gilbert, described by White and Sprague in 1929[33] who, with the tetralogy of Fallot, survived to the age of 59 years and 8 months.

Finally, it is noteworthy that she had no actual heart failure until a few months before her death and that her cerebral circulation was maintained satisfactorily until a few weeks before she died when she began to have syncopal attacks.

Summary

We have reported herein the case of a woman with congenital pulmonary stenosis with a patent foramen ovale who survived to the age of 75 and who lived a useful life, death finally occurring a few months after the beginning of failure of the right ventricle associated with insufficiency of the cerebral circulation. The oldest case proved at autopsy previously recorded died at the age of 57.

Appendix

Of 8 cases of pulmonary stenosis recently reported by Allanby and Campbell,[34] 7 of which were autopsied, 4 showed patency of the foramen ovale in addition. The oldest case was a woman aged 29 at death.

ACKNOWLEDGEMENT

The authors take pleasure in thanking Dr. R. S. Schaaf for his aid in looking up some of the historical references to this condition.

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Pulmonary Artery Aneurysms

Report of a Case Treated by Surgical Intervention

By Brian Blades, M.D., William Ford, M.D., and Patrick Clark, M.D.

The successful surgical treatment of an aneurysm of the left main pulmonary artery is reported. It appears that, after ligation of the main pulmonary artery, it is desirable not to remove the lung but preserve it as a space occupying organ which will retain some function. Literature on the subject of pulmonary aneurysms is reviewed.

PULMONARY ARTERY aneurysms are relatively rare lesions. One hundred and fifty-two cases have been found in world literature. The purpose of this communication is to review briefly available information on the subject and to report a case in which successful surgical treatment has been achieved.

Boyd and McGavack,[1] in 1939, reported 111 cases of pulmonary aneurysm proved at necropsy. In 1947, Deterling and Clagett[2] added 36 cases in their excellent paper on this subject. Five more authenticated cases reported since 1947 may be added to the list. In 1946, Thompson and Gerstl[3] recorded a case which was not included in the bibliography of Deterling and Clagett. Since 1947, Dotter and Steinberg[4] have reported two cases and Lillian[5] has had one case. Available evidence indicates that one aneurysm of the pulmonary artery may be found in approximately 14,000 necropsies.

Jules,[6] Breslin[7] and others have described the symptoms of pulmonary aneurysm which include dyspnea, cough and hemoptysis. These manifestations of the disease may occur early. Chest pain, cyanosis, edema, ascites and clubbing of the fingers are late manifestations. Tachycardia is sometimes evident with associated polycythemia. Roentgenograms of the chest often reveal a well delineated hilar shadow and hypertrophy of the right heart may be found. Pezzi's sign of hilar dance caused by transmission of an expansile pulsation may be observed. The lesion can usually be delineated by angiocardiography.

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Aneurysms of the pulmonary artery occur in a younger age group than aortic aneurysms. The sex incidence is about equal. Aneurysms of the left pulmonary artery are more common than those on the right.

The etiology of pulmonary artery aneurysms is not understood, but it might be safe to assume that conditions which raise the pulmonary arterial pressure may cause dilatation of the vessels. Important contributory effects, therefore, might result from a patent ductus arteriosus, mitral stenosis, interauricular septal defects and other congenital anomalies. Deterling and Clagett[2] concluded that pulmonary aneurysms have a congenital origin in about 47 per cent of the cases they studied. Boyd and McGavack[1] were of the same opinion.

Miscellaneous etiologic factors which have been considered include syphilis, arteriosclerosis, trauma, subacute bacterial endocarditis, tuberculosis and atheroma. Earlier writers on the subject believed that syphilis was a probable etiologic factor in about one-third of the cases. This conclusion might be questioned.

It is important to note that about one-third of the cases of pulmonary aneurysm die from sudden rupture of the lesion. It is apparent, therefore, that this condition deserves prompt and adequate surgical treatment if possible. A notable exception is a patient described by Mason[8] in 1938, who has been observed for 17 years and has suffered no ill effects from the lesion.

Case History

A 59-year old white man, a welder by trade, was admitted to the George Washington University Hospital on Sept. 27, 1949. His only complaint was that seven weeks before admission he coughed and

blood was apparent, but never in great amounts. There were no complaints of chest pain, dyspnea, fatigue or anorexia.

The past history revealed that the patient had had typhoid fever at the age of 10, which was complicated by pneumonia. He also had been troubled with attacks of acute sinusitis in the past. The family history was significant in that one brother had had pulmonary tuberculosis.

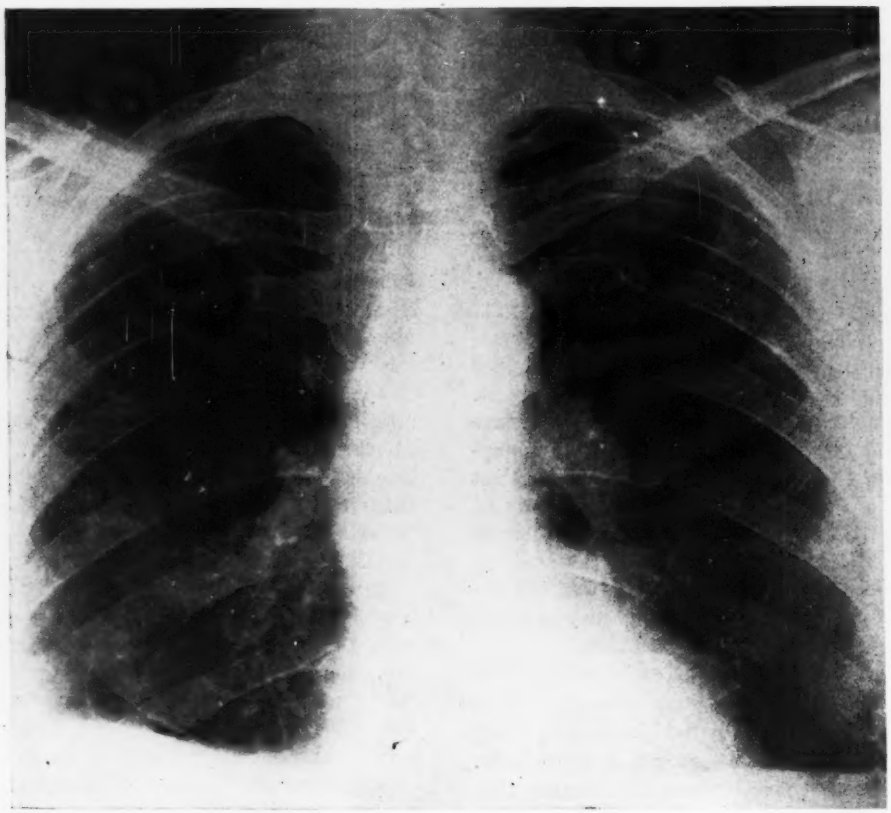

FIG. 1. Frontal projection demonstrating a prominent left hilar shadow with density extending upward.

The patient was a well developed, well nourished white man. Temperature, pulse and respiratory rates were normal. The blood pressure was 150/90. The anteroposterior depth of the chest wall was increased. Breath sounds were somewhat distant and there was some question of early emphysema.

Examinations of the blood and urine were within normal limits and repeated serologic tests for syphilis were negative.

Roentgen examination of the chest on Sept. 28, 1949, revealed a prominent shadow at the level of the left hilum with the density extending somewhat upward. The diaphragms were flat and the roentgen appearance of the chest suggested early emphysema (figs. 1 and 2). Visualization of the tracheobronchial tree with lipiodol was not helpful.

Examination through the bronchoscope revealed a normal tracheobronchial tree. Bronchial washings were negative for acid fast bacilli but, on one occasion, the Papanicolaou test revealed cells which were considered suspicious of tumor. All other washings were negative. An electrocardiogram demonstrated slight right ventricular strain.

Immediately after these examinations the patient stopped coughing up blood-streaked sputum and returned to his home. Hemoptysis recurred, however, the following month and again in February of 1950 when he had a severe attack of hemoptysis and it is estimated that he coughed up about 200 cc. of blood. During the same period he developed dyspnea on exertion.

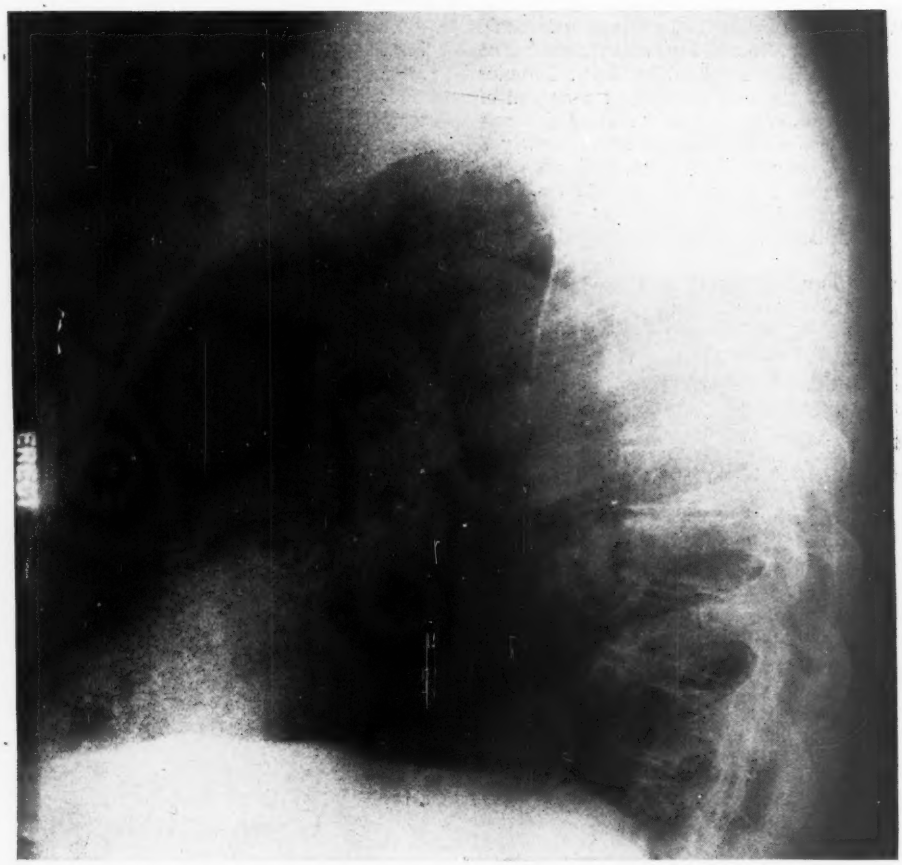

FIG. 2. Lateral view showing the midthoracic lesion.

Roentgen examination of the chest at that time revealed enlargement of the shadow at the left hilum. Examinations with the bronchoscope were again negative, but a suspicious Papanicolaou stain was obtained.

During this period of study, the possibility of an aneurysm of the left pulmonary artery was considered because of the odd configuration of the shadow. It must be admitted, however, that this possibility was dismissed in favor of the diagnosis of bronchiogenic carcinoma and angiocardiography was not done.

Preoperative studies of the blood, urine and proteins were normal. The bleeding, clotting and prothrombin times were normal. The vital capacity was 72 per cent of the expected measurement and another electrocardiogram revealed evidence of right ventricular strain.

Operation: The left chest was entered through a posterolateral incision at the level of the fifth rib.

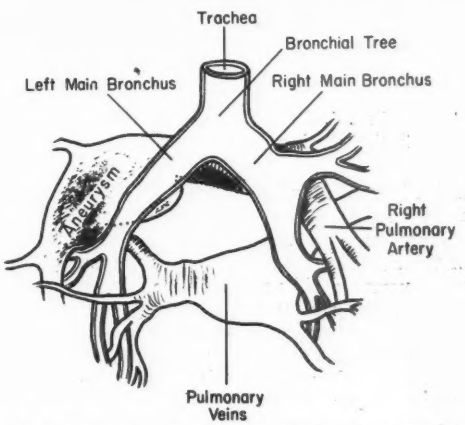

FIG. 3. Drawing of posterior-anterior view showing relative size, shape and position of aneurysm.

After the lung was exposed, a few lymph nodes could be seen and palpated at the level of the hilum but no mass was palpable in the lung itself. Anterior displacement of the lung revealed an aneurysm of the left pulmonary artery (fig. 3). The lesion was elliptical in shape and measured approximately 7 cm. in length and was about 5 cm. in depth at its center. The origin of the sac was about 2 cm. from the main trunk of the left pulmonary artery and extended well below the artery to the dorsal division of the lower lobe ending at the level of the artery to the basal division.

Since the origin of the aneurysm was at the level of the upper lobe arteries, it became apparent that these vessels could not be saved. Accordingly, the left pulmonary artery was ligated and divided proximal to the aneurysm and each branch of the artery arising from the aneurysm was ligated. The lesion was tightly adherent to the left lower lobe bronchus and it appeared that erosion had occurred at this level. Since the aneurysm was completely excluded from the pulmonary circulation, the sac was not removed.

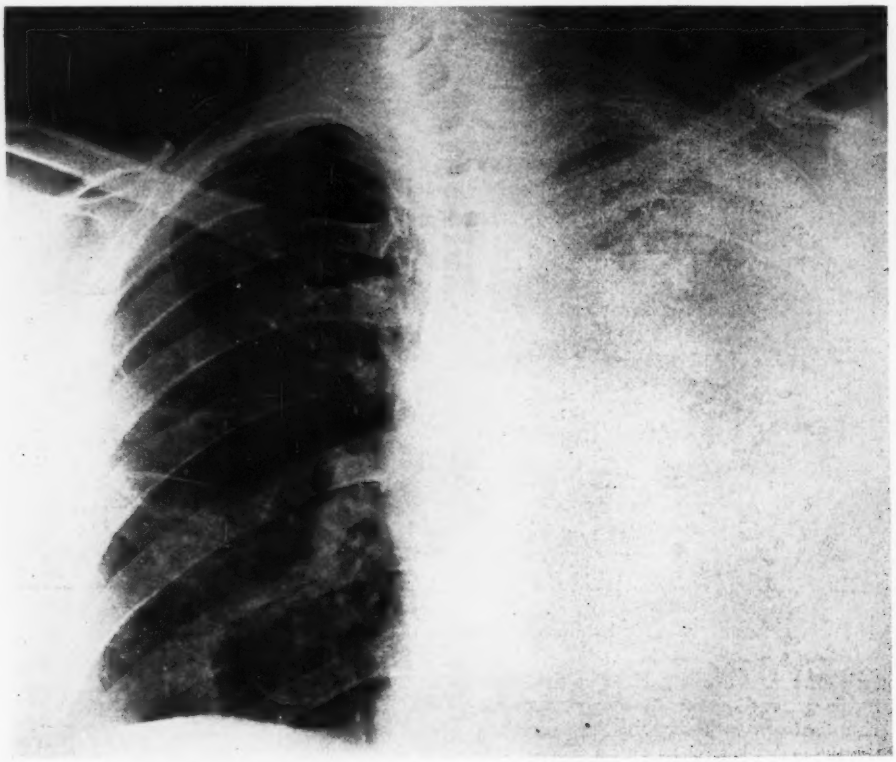

FIG. 4. Frontal projection taken one week after operation demonstrating generalized density in the left chest.

The lung was not removed. The reasons for leaving the organ after ligation of the left pulmonary artery will be discussed later.

On the first day after operation the patient's temperature was 40 C. and remained at rather high levels for four days and finally fell to normal on the eleventh day after the operation. During this period there was no evidence of a wound infection, infection of the urine or other sources of temperature elevation outside of the chest itself. The pulse rate was also elevated and varied from 130 to 140 for three days. On the tenth postoperative day the pulse rate had stabilized at 90. Early examinations with the electrocardiogram revealed the right ventricular strain, which had been evident before the operation, and sinus tachycardia. Roentgenograms of the chest taken at daily intervals demonstrated a gradually increasing density over the entire left lung field. After a week the density in the apex of the lung began to clear (figs. 4 and 5).

Before operation the volume of packed red cells was 48 mm. but by March 6, ten days after surgical intervention, the packed red cells had fallen to 37

mm. in spite of transfusions of 1000 cc. of whole blood. It seems unlikely that this sharp reduction resulted from the deterioration of transfused red cells. The leukocyte count was 12,850 on the first postoperative day and quickly fell to normal limits. Repeated attempts at thoracentesis secured only small amounts of blood-stained fluid which was sterile. It seemed apparent, therefore, that the haziness over the left chest was not entirely the result of accumulated pleural fluid.

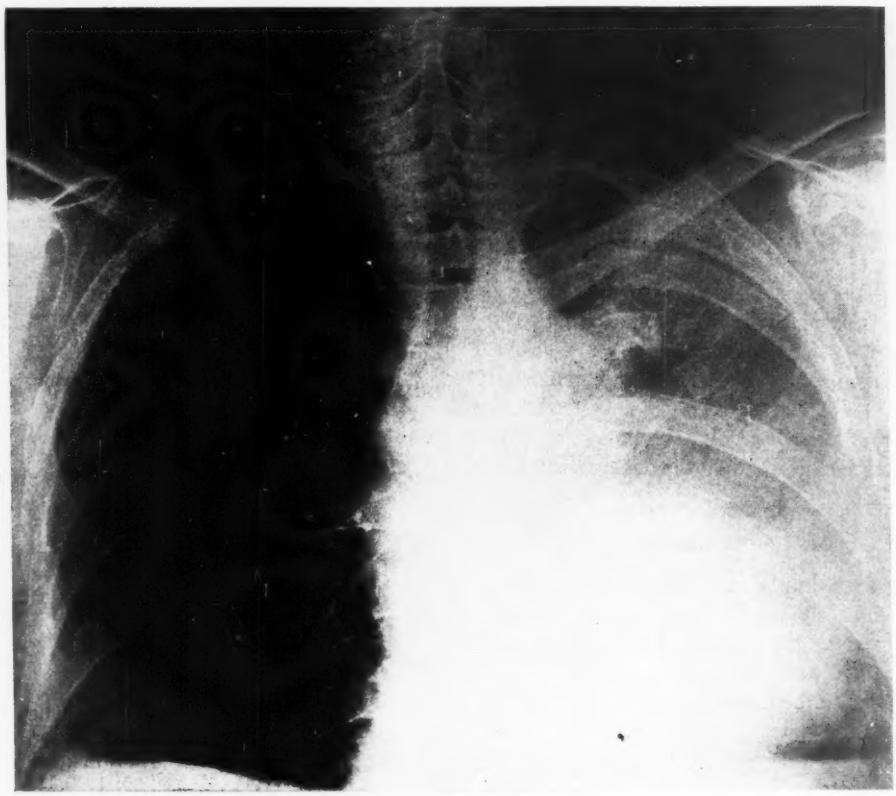

FIG. 5. Frontal projection taken two weeks after operation demonstrating clearing in left apex.

The patient left the hospital on the eleventh postoperative day and has been seen at frequent intervals as an out patient. Three weeks after the operation a roentgenogram of the chest showed significant clearing of the opacity which was noted from the time of operation. On this same date an electrocardiogram was obtained and did not show right ventricular strain. The patient's temperature was normal and he had a full and regular pulse in the neighborhood of 96 per minute. His appetite was good. His only complaint was slight dyspnea on exertion. Four weeks after the operation the patient had begun to gain weight, was afebrile, and his only complaint continued to be slight dyspnea after exercise.

COMMENT

A decision was made in our case not to remove the lung after ligation of the artery. The patient appeared to have moderate emphysema and the presence of a space occupying organ on the left side might prevent serious overdistension of the right lung at a later date. Moreover, no evidence indicated the necessity of pneumonectomy after division of a main pulmonary artery.

Wilms and Sauerbruch[9] demonstrated that the ligation of the pulmonary artery in rabbits and dogs did not cause death; and Rienhoff[10]

has employed pulmonary artery ligation as a preliminary to total pneumonectomy in poor risk patients.

Janton, Redondo and Scott[11] have studied a patient in whom accidental ligation of the left pulmonary artery was done. They found that carbon dioxide and oxygen values were 3.74 per cent and 19.14 per cent, respectively, as compared to 1.65 per cent and 10.15 per cent for the other side. The observations of Roche and his co-workers[12] in a similar case in which the left pulmonary artery had been ligated to control hemorrhage during the performance of an operation on a patent ductus, were in general agreement with those of Janton and his co-workers. They also found that the right pulmonary artery and right heart chambers had normal pressures when determined by cardiac catheterization.

Bloomer and Harrison,[13] in experiments on animals, concluded that gas exchange after pulmonary artery ligation is the result of blood flow in anastomoses between the pulmonary artery and the pulmonary capillary bed. They employed bronchospirometry, blood oxygen determinations and cardiac output studies in their experiment.

Conclusion

Since accumulated evidence indicates that approximately one-third of the patients with aneurysms of the pulmonary artery die of sudden severe hemoptysis from rupture of the aneurysm, it becomes apparent that these lesions should be treated by surgical intervention whenever a positive or tentative diagnosis has been made.

Experimental evidence and recent experience in the treatment of a case of pulmonary artery aneurysm indicates that it is not necessary to remove the lung after ligation of the main pulmonary artery and, moreover, it is probably desirable to leave the organ in the body as living, space filling tissue which retains some of its function.

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Electrokymographic Studies of the Left Atrium in Normal and Diseased Hearts

By J. B. McKinnon, M.D., and Ben Friedman, M.D.

Electrokymographic tracings of left auricular pulsations in normal and diseased states are described. A characteristic abnormality observed in persons with organic mitral valve insufficiency is believed to be graphic evidence of regurgitation of blood from ventricle into atrium. Electrokymographic evidence of regurgitation was found in persons with mitral stenosis without an audible systolic murmur but instances of mitral stenosis without insufficiency were recorded. Patients with Austin Flint murmurs and individuals with murmurs mimicking mitral insufficiency showed uniformly normal atrial pulsations.

THE ELECTROKYMOGRAPH is an instrument which makes continuous recordings of pulsations observed under the fluoroscope. The mechanical aspects of this device and its clinical application have been the subjects of recent reviews.[1–5] Interpretation of the records is frequently difficult due to vigorous positional movements of the heart which obscure the actual volume changes. This difficulty is especially prominent in the movements of the right atrium and the ventricles. The left atrium is so situated that it partakes to a lesser degree of the vigorous positional movements of the heart. In our experience, tracings can be obtained of this chamber which appear to show changes associated with events in the cardiac cycle. It must be pointed out, however, that extreme care has to be employed in the interpretation of the records. Many artefacts may arise by improper positioning of the recording slit, resulting in changes which are due to mixed pulsations of a variety of structures within the chest. Errors will occur less frequently in the hands of a fluoroscopist who has experience in the use of the electrokymogram.

The pulsations of the left atrium may be recorded in either the right or the left anterior oblique position. There is some difference in the appearance of the tracings; the systolic filling wave recorded in the right oblique position is more prominent than that taken in the left oblique position. The tracings discussed in this paper were taken with the patient erect in the right anterior oblique position, employing a 60-cycle half wave fluoroscope and a Cambridge electrokymograph and recording device. In this position a downward deflection in the curve represents volume contraction or movement of the heart in the direction of the apex, while upward deflection will result from atrial expansion or movement of the heart in the direction of the base.

The normal left atrial curve usually consists of three waves: one in atrial systole and two in atrial diastole (fig. 1). In some instances the two diastolic waves tend to merge. The first wave begins with the onset of the first heart sound and consists of a small upward deflection of brief duration, which returns promptly to the baseline. This is followed by progressive elevation in the baseline (wave 2) which continues until immediately after the second heart sound, at which time it drops off sharply until about the middle of diastole. At this point it may level again or actually rise somewhat, and, shortly thereafter, decline again (wave 3) because of active atrial contraction.

The small upward deflection coincident with first sound (wave 1) is believed to be due to two factors: (1), a hypothetically small amount of regurgitation as the mitral valve is closing, and (2), the elastic effect of the sudden stretch of the mitral valve with the beginning of the isometric phase of ventricular systole. Evidence

From the Veterans Administration Hospital, McKinney, Texas.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the results of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

in favor of the latter interpretation is afforded by the study of a patient who had auricular fibrillation without demonstrable organic cardiac disease (fig. 2). In this tracing the size of the first wave varies directly with the force of the ventricular contraction, as measured by the height of the carotid pulse wave. The downward deflection of the first wave occurs in the ejection phase of ventricular systole and is believed to represent movement of the atrioventricular septum and the attached atrium toward the apex. It varies in depth and duration depending on whether atrial filling or ventricular contraction dominates the movement. Atrial filling, which occurs simultaneously with ventricular systole but results in diametrically opposite deflection in the atrial tracing, is mainly responsible for the upward deflection of the second wave. The point of change in direction at the peak of wave 2 occurs shortly after the second heart sound and indicates the opening of the mitral valve. The subsequent decline in the curve represents emptying of the atrium during the course of passive filling of the left ventricle. This continues until the middle of ventricular diastole at which point the atrial and ventricular pressures approximate each other and emptying of the atrium stops. The atrial volume remains unchanged or may even be increased slightly until active contraction completes the emptying of the atrium. The third wave is absent in cases of auricular fibrillation (fig. 3). Volume changes as a result of active atrial contraction appear generally to be

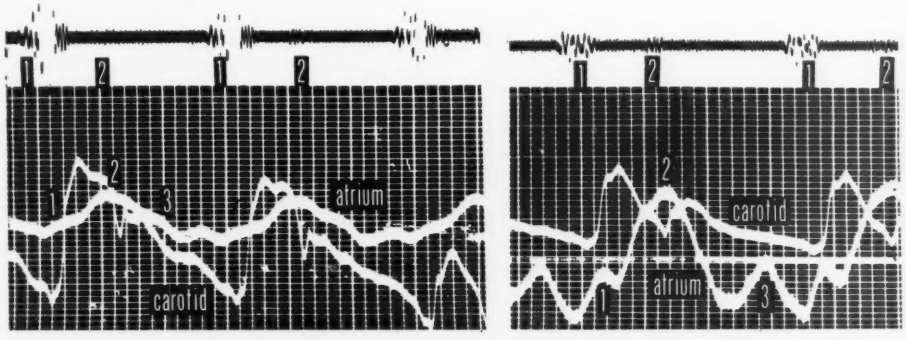

FIG. 1. *Left:* A 46 year old man with severe emphysema, right axis shift in electrocardiogram and right ventricular enlargement. No congestive failure. Note normal atrial tracing with waves 1 and 2 fused. *Right:* Normal subject.

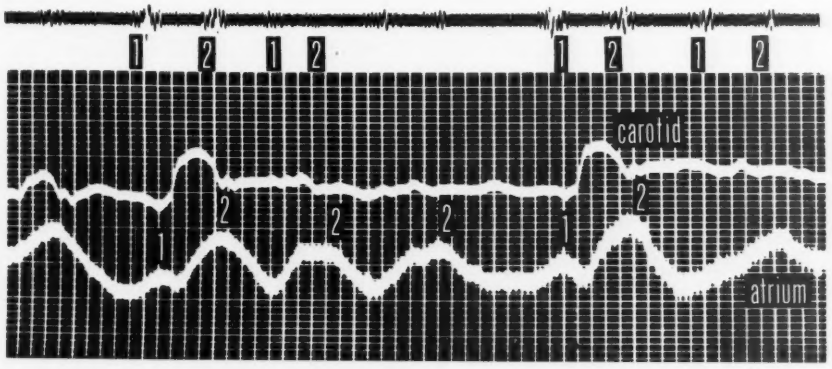

FIG. 2. 30 year old man with auricular fibrillation and no evidence of valvular or other organic heart disease. Note the prominent first wave associated with forceful beats. Electrokymographic tracings taken after normal sinus rhythm was restored showed a normal atrial curve.

small. In some normal patients wave 3 may be absent or appear to blend with the preceding wave. Study of the left atrial curve in one patient with complete heart block similarly demonstrated that the volume of ejection of the left atrium during atrial contraction is extremely small in proportion to that occurring during the passive filling phase of the cycle. These observations are in conformity with the conclusions based on the direct measurements of atrial and ventricular pressure and volume changes.[6]

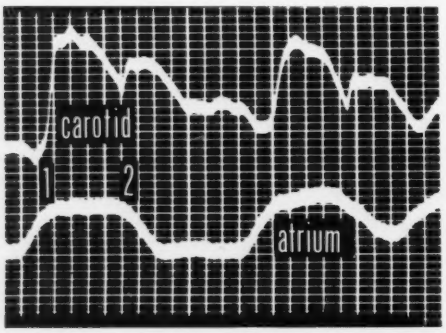

FIG. 3. A 31 year old man with diastolic rumbling murmur at the apex, auricular fibrillation, congestive heart failure, marked left atrial enlargement and calcification of the mitral valve. A systolic murmur was not heard. Note curve of mitral regurgitation and absence of wave 3.

TABLE 1.—*Type of Atrial Tracings in Selected Subjects*

Clinical Diagnosis	Number of Patients	Normal Tracing	Abnormal Tracing
Normal heart	25*	25	0
Organic mitral valve disease			
Mitral stenosis	8	3	5
Mitral insufficiency	2	0	2
Mitral stenosis and insufficiency	9	3†	6
Syphilitic aortic insufficiency and Austin Flint murmur	3	3	0
Functional mitral insufficiency with organic heart disease	8	8	0
Cor pulmonale	6	6	0
Other types of organic heart disease	14	14	0

* Two with apical systolic murmurs but no circulatory abnormalities.

† Two tracings are classified as borderline (see text).

A characteristic abnormality in the tracing recorded from the left atrium in cases of mitral valve disease has been described by Luisada and Fleischner.[7] This consists of a marked elevation of the systolic wave, producing a systolic "plateau." They observed the characteristic changes in all cases of mitral valve disease, whether of mitral insufficiency, mitral stenosis, or stenosis and insufficiency combined.

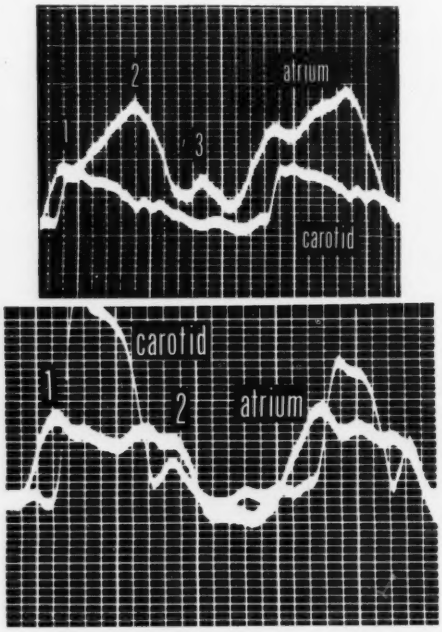

FIG. 4. *Above:* 25 year old student had an illness characterized by low grade fever, malaise, weakness, a changing P-R interval and favorable response to salicylates. A faint presystolic low pitched apical murmur was heard. No systolic murmur and no enlargement of cardiac chambers was detected. Note diminution in the downward deflection of wave 1. This is a transition to a positive systolic plateau (shown below).

Below: 51 year old man with mitral stenosis and insufficiency, auricular fibrillation and congestive heart failure. The left atrium was enlarged. Note sustained elevation of atrial curve until a point beyond closing of the aortic valves. Carotid pulse tracing lags .03 to .04 sec. behind atrial electrokymogram.

We have examined 19 patients with mitral valve disease. On the basis of physical signs 9 of these subjects had mitral stenosis and insufficiency, 7 had mitral stenosis alone, and 2 individuals had mitral insufficiency alone.

In general, our findings have agreed with those of Luisada and Fleischner (table 1). Tracings recorded in 11 patients with organic mitral insufficiency were abnormal in 8, borderline in 2 and normal in 1 instance. The borderline tracings were obtained in 2 subjects with far-advanced mitral stenosis and congestive heart failure, the normal tracing in a young man with early mitral stenosis and a faint grade 1 systolic apical murmur. Five of the 8 patients presenting only apical diastolic murmurs without audible systolic murmurs showed abnormal records characteristic of mitral insufficiency (fig. 3). However, in 3 patients who had the physical signs of mitral stenosis without mitral insufficiency, a normal left atrial curve was recorded. In very early valve lesions (fig. 4, top) the first abnormality to be noted is moderate elevation of the first wave, which then levels off and becomes a slowly rising curve throughout the rest of systole. In more advanced valve lesions the regurgitation appears to persist throughout systole and sometimes beyond the closing of the aortic valves (fig. 4, bottom) as evidenced by sustained elevation of the systolic wave. In 2 patients with very far advanced mitral stenosis, cardiac enlargement, marked enlargement of the left atrium and congestive failure, a different configuration appears (fig. 5) in that the atrial filling curves tend to resemble those seen in the normal state.

Normal tracings were observed in each of 8 patients with so-called "functional" mitral insufficiency, as manifested by apical systolic murmurs, grades 2 to 3 in intensity, in the presence of nonvalvular heart disease with well defined cardiac enlargement (fig. 6). The etiologic agents responsible for the heart disease in these 8 instances were coronary arteriosclerosis in 3 cases, hypertension in 2 patients, and thyrotoxicosis, diffuse myocarditis and anemia with hypertension of chronic nephritis each in one individual. Three patients with aortic insufficiency and an Austin Flint murmur showed no electrokymographic evidence of mitral insufficiency.

Normal atrial curves were recorded also in 2 healthy subjects with no clinical evidence of cardiac or circulatory abnormalities but with

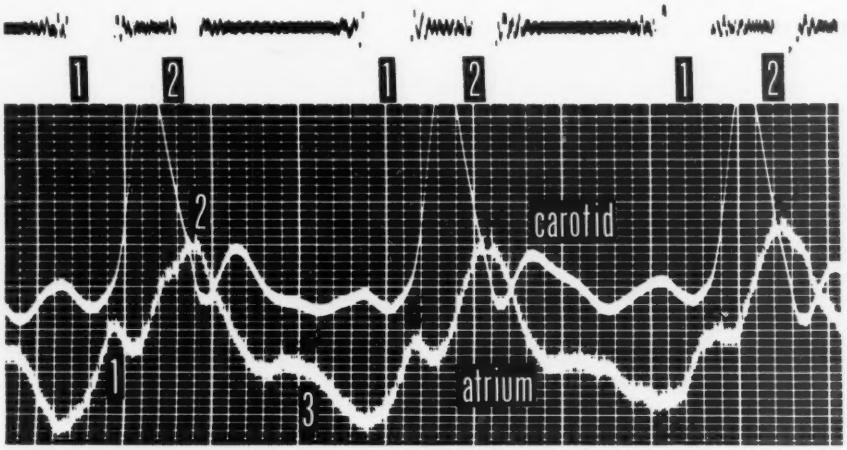

FIG. 5. A 46 year old man with congestive heart failure, auricular fibrillation, a rumbling diastolic murmur and loud blowing apical systolic murmurs. The patient died shortly after this record was taken. Autopsy disclosed severe "fish-mouth" mitral stenosis with calcification. Atrial tracing shows only slight abnormality.

apical murmurs of grade 1 to 2 intensity based on the classification of Levine.[8] Six patients with cor pulmonale and 14 individuals with other types of organic cardiac disorders showed normal configurations in the atrial pulsation.

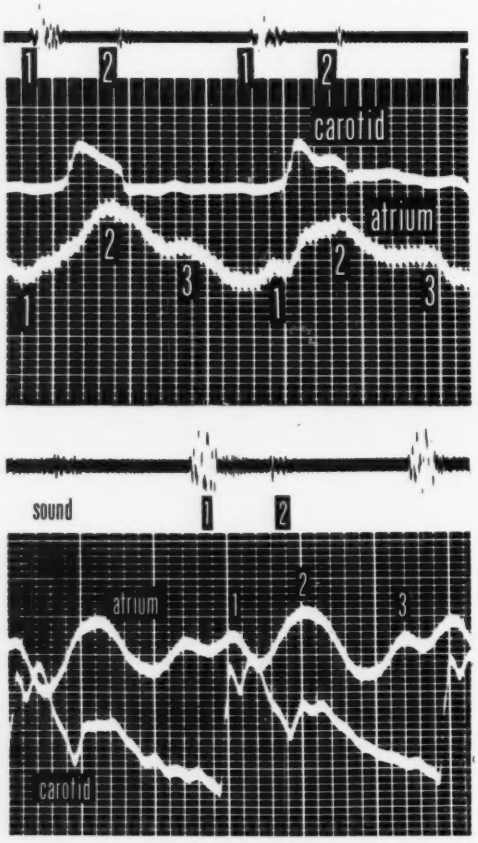

FIG. 6. *Above:* A 54 year old man with arteriosclerotic coronary disease, marked cardiac enlargement, congestive heart failure and a grade 2 to 3 systolic murmur at the apex. There was no hypertension, anemia or fever. Note normal atrial curve with presumed "functional mitral insufficiency." *Below:* 26 year old man with hyperthyroidism (basal metabolic rate + 42 per cent), moderate cardiac enlargement, grade 2 murmur at the apex.

DISCUSSION

The essential feature of the abnormality in the left atrial volume curve in persons with mitral valve disease is an increased filling at the beginning of the isometric contraction phase of ventricular systole. It can be attributed neither to artefacts due to filling of pulmonary veins or aorta nor to transmitted ventricular thrusts, for it precedes these events in the cardiac cycle by at least .06 second. Moreover, it does not appear in tracings taken in normal subjects or in patients with nonvalvular heart disease. The possibility exists that the right ventricular hypertrophy which usually accompanies mitral valve disease might be responsible for a positional change by reason of more forceful contraction. Thus the typical deformity in the tracings might conceivably have no relation to regurgitation of blood but might be related to secondary changes incidental to right ventricular strain. To evaluate this possibility, we examined 6 patients with varying degrees of right ventricular strain secondary to chronic pulmonary disease. In none of these patients was an abnormal atrial curve observed. We believe, therefore, that this abnormality of the atrial filling curve seen in persons with mitral valve disease does actually represent regurgitation of blood through an insufficient valve. The abnormal tracing resembles the auricular volume curves recorded by Wiggers and Feil[9] in experimental acute mitral valve insufficiency.

There are two possible explanations for the tendency for the appearance of a normal pattern in persons with far advanced mitral stenosis: (1) When the mitral orifice is greatly narrowed, there may be very little regurgitation. This seemed to be the situation in one of the patients who came to autopsy (Fig. 6). (2) The high atrial pressure and reduced left ventricular pressure which accompanies advanced mitral stenosis results in a decline in pressure differential between the left ventricle and left atrium. This factor probably plays a minor role, since the ventriculoatrial pressure gradients in congestive failure are still very high during the phase of ventricular ejection.

The evidence supports the belief that mitral stenosis does occur without regurgitation, but that the absence of an audible systolic murmur in persons with mitral stenosis does not rule out the simultaneous existence of mitral regurgitation.

The apical systolic murmurs which appear in persons with left ventricular dilatation due

to nonvalvular heart disease have been commonly attributed to functional regurgitation as a result of dilatation of the mitral ring or to displacement of the papillary muscles and cordae tendinae to which the valve cusps are attached. The failure to demonstrate abnormal atrial pulsations in conditions where functional mitral insufficiency would be anticipated may be due to the insensitivity of the method of detecting small degrees of regurgitation. In persons with known mitral valve disease, electrokymographic evidence of regurgitation has been detected in 5 instances without an audible systolic murmur and in others with murmurs of grade 1 or 2 intensity. The finding of normal atrial pulsations in individuals with nonvalvular heart disease and loud systolic murmurs suggests that the murmurs are not due to mitral insufficiency or else that, if actual regurgitation is present, it is slight and not related to the intensity of the murmur.

The clinical diagnosis of mitral insufficiency has been based heretofore on indirect evidence, dependent principally upon the presence of an apical systolic murmur. The diagnosis is frequently in doubt, particularly when there is no evidence of associated mitral stenosis. Any procedure which reflects hemodynamic changes related directly to valvular insufficiency should prove to be of great value. Alteration in the electrokymographic tracings of left auricular movement in persons with diseased mitral valves are of a character which can be explained only on the basis of actual regurgitation of blood from the ventricle into the auricle.

This new tool should prove to be value in the study of a variety of problems. These include: (a) evaluation of the significance of apical systolic murmurs, (b) the progression of mitral valve disease, (c) detection of mitral stenosis in the rare cases when the diastolic murmur is inaudible, and (d) differentiation of the Austin Flint murmur from that of organic mitral stenosis.

Summary

(1) The normal left atrial pulsation, as recorded by the electrokymograph, has been described.

(2) A characteristic abnormality in the tracing was observed in cases of mitral valve insufficiency.

(3) This abnormality is not due to forceful contraction of the right ventricle, but is believed to be related to actual regurgitation of blood into the left atrium. The abnormality of the curve tended to be less pronounced in two subjects with very far advanced mitral stenosis and congestive failure. This is attributed mainly to marked diminution in size of the mitral orifice and hence in the degree of regurgitation.

(4) Electrokymographic evidence of regurgitation was found in persons with mitral stenosis without a systolic murmur. Instances of mitral stenosis were observed without clinical or electrokymographic evidence of regurgitation.

(5) Patients with the Austin Flint murmur and subjects with nonvalvular heart disease with or without apical systolic murmurs showed uniformly normal atrial tracings. The absence of confirmatory evidence of regurgitation in persons with nonvalvular heart disease and loud apical systolic murmurs cast considerable doubt on the concept of functional mitral insufficiency as the cause of the murmurs.

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Normal Esophageal and Gastric Electrocardiograms

Description, Statistical Analysis and Bearing on Theories of "Electrocardiographic Position"

By ALBERT D. KISTIN, M.D., WARREN D. BRILL, M.D., AND GEORGE P. ROBB, M.D.

An analysis of normal esophageal and gastric electrocardiograms is presented. Some standards of abnormality in the literature are found to be unacceptable, principally with reference to Q and the diagnosis of infarction. The study of leads facing the dorsal and diaphragmatic cardiac surfaces seems to be a suitable test of current concepts of "electrocardiographic position." Some of these concepts are supported by this study, but others are questioned.

ALTHOUGH esophageal and gastric electrocardiograms have been employed in a number of theoretic and clinical studies, there is still inadequate information concerning the characteristics and the range of variation of these electrocardiograms in normal individuals. This is an analysis of such electrocardiograms of 50 men without clinical evidence of heart disease.

Cremer[11] and Kraus and Nicolai[24] first mentioned the use of esophageal leads, and subsequent studies were carried out by Baur and Böhme,[5] Lieberson and Liberson,[29] Howard,[21] Brown,[6, 7] Luisada,[31] Hamilton and Nyboer,[18] Helm, Helm and Wolferth,[20] Carlos Rubio,[10] Myers and Klein[36] and others.[1,12,19,34,39,40,41,47,48,49]

MATERIAL AND METHODS

The subjects were 50 male hospital employees or ambulatory patients 20 to 50 years old examined by the authors for this study and showing no evidence of past or present heart disease, diphtheria, rheumatic fever, syphilis, hypertension, thyroid disease, severe malnutrition, anemia, chest pain, pulmonary disease, chest deformity, renal disease or malignancy. A roentgenogram of the chest was obtained in each case; blood count, urinalysis, circulation time (calcium gluconate) and serologic test for syphilis were obtained in all patients and all but a few of the employees.

Standard limb leads, six precordial leads (V_1 through V_6), augmented unipolar extremity leads,[16] and a series of fifteen esophageal and gastric leads were obtained in each case with the subject supine. The indifferent electrode for the precordial, esophageal and gastric leads was that of Wilson[52] or in some cases the Goldberger modification.[16] The esophageal and gastric leads were obtained with a modified Nyboer tube,* the exploring electrode placed 25 to 60 cm. from the nares at 2.5 cm. intervals, actual distances varying from those used in the text up to plus 0.6 cm. and minus 0.8 cm. Sanborn Cardiette and Viso-Cardiette and Technichon three channel instruments were used.

With rare exceptions at least three complexes were measured with a hand lens providing five times magnification, and averaged. Amplitudes were estimated to the closest 0.25 mm. and corrected for standardization, and time intervals were estimated to the closest 0.01 second. Accepted terminology and methods of measurement were employed.[3]

To correlate electrode positions with electrocardiograms, anteroposterior and lateral roen-

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

* Manufactured by C. R. Bard Inc.

grams were obtained immediately after completion of the electrocardiograms with the subject supine, the breath held during quiet respiration, and the distal electrode 60 cm. from the nares (fig. 1).

"Statistically highly significant" indicates a probability of less than one in one hundred that compared data are from the same population, and "statistically significant," that this probability is greater than one but less than five in one hundred.

may be placed closer to the heart here than in any other location in the intact human being; it is estimated that an electrode may lie as close as 0.5 to 1 cm. from the dorsal wall of the left atrium. According to the descriptions and illustrations in several anatomy texts, of which figure 2 is representative, the lower end of the esophagus is dorsal to the left ventricle. It is apparent, however, from figure 2 that the interventricular sulcus is close to the lower end of the esophagus, and it may be expected that

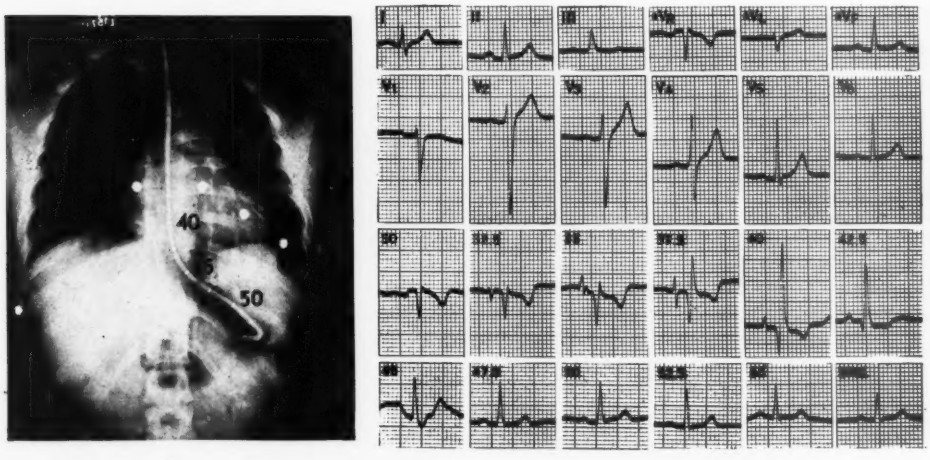

FIG. 1. The roentgenogram and the electrocardiograms in one of the cases. The radiopaque tube and the electrodes mounted on it are shown. The roentgenogram was obtained with the subject supine. Three of the exploring electrode positions, 40, 45, and 50 cm. from the nares, are indicated on the roentgenogram. The electrocardiograms derived from these electrode positions are designated by the same numbers. The opaque markers across the chest show the exploring electrode positions for the precordial leads.

Artefacts

Artefacts occur frequently in these leads, probably due to peristalsis, respiration, swallowing, poor contact and motion of the heart; T and RS-T are distorted more than QRS. In a few cases roentgenograms showed the tube doubled up in the esophagus producing a discrepancy between actual position of the exploring electrode and apparent position as estimated from tube markings.

ANATOMIC RELATIONS

Part of the esophagus lies dorsal to the pericardium covering the left atrium (fig. 2). Except for the direct intracardiac leads an electrode

slight changes in cardiac position might bring the interventricular sulcus or the right ventricle into relation with this part of the esophagus. Some electrocardiographic evidence that the latter occasionally occurs will be presented.

In the dissection illustrated in figure 2 the true posterior or dorsal surface of the heart consists largely of left atrium. The ventricles do contribute to the posterior surface, but much of the ventricular surface lies on the diaphragm. The cross sections reproduced in figure 2 from Eycleshymer and Shoemaker[13] happen to be the same distance apart as the electrodes on the tubes we used, namely, 2.5 cm. There is but a single level, the one immediately above

the diaphragm passing through the intervertebral disc between the ninth and tenth thoracic vertebrae, in which the esophagus lies immediately behind left ventricle. The two levels above this show esophagus immediately behind left atrium. In the level passing through the eighth

The Position of the Exploring Electrode and the Various Levels

Correlation of the electrocardiograms with the roentgenograms confirms the observations of others[5, 6] that P waves with an intrinsic

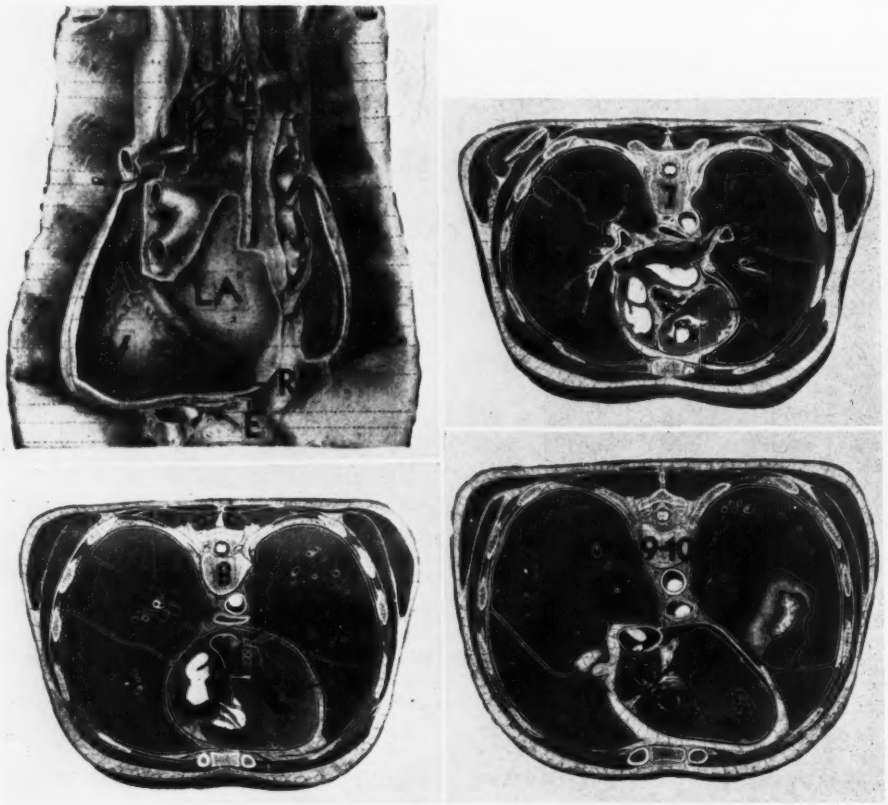

Fig. 2. Posterior (dorsal) view of the heart from Morris' Human Anatomy,[33] and cross-sections of the body from Eycleshymer and Shoemaker.[13] *E*, esophagus; *LA*, left atrium; *LV*, left ventricle; *RV*, right ventricle; *7*, body of seventh thoracic vertebra; *8*, body of eighth thoracic vertebra; *9* and *10*, intervertebral disc between the ninth and tenth thoracic vertebra. The cross sections illustrate levels 2.5 cm. apart. (*By courtesy of Dr. J. P. Schaeffer, The Blakiston Co., and D. Appleton and Co.*)

thoracic vertebra the left ventricle is some distance to the left of the esophagus. It is to be expected that these cross sections would appear somewhat different with different cardiac positions, but some discussions of esophageal leads tend to exaggerate the extent of dorsal wall of ventricle believed to lie immediately ventral to the lower end of the esophagus.

deflection[26, 27, 50, 51] are obtained when the exploring electrode is at positions opposite the left atrium. These positions may be referred to as *atrial* levels and the leads obtained from them as atrial leads. In addition to an approximate qualitative judgment of the position of the left atrium from the cardiac shadow, the position of the electrode was correlated with the

vertebral bodies. The left atrium is described as extending across the levels of the bodies of the fifth to the ninth thoracic vertebrae.[33] In 36 of the 43 cases in which roentgenograms were available, these electrode positions lay between the levels of the bodies of the fifth to the ninth thoracic vertebrae although they frequently did not extend over the entire range. In 1 case a P wave with an intrinsic deflection was obtained from an electrode position opposite the fourth thoracic vertebra and in 6 cases an intrinsic deflection was still obtained when the exploring electrode lay opposite the tenth thoracic vertebra.

The observed range of the atrial levels extended from 32.5 to 47.5 cm. from the nares. Atrial levels were found at 40 cm. in 49 of the 50 subjects, at 37.5 to 40 cm. in 47 and from 35 to 40 cm. inclusive in 34 of the subjects. The mean highest atrial level was at 35.3 cm. and the mean lowest atrial level at 42.2 cm. These values approximate those previously recorded[1, 9, 32, 34, 40] but differ somewhat. There was a slight tendency for the atrial levels to be grouped further from the nares in taller individuals, but the variation was considerably less than that of the heights which ranged between 63 and 74¾ inches.

In leads obtained with the exploring electrode at a variable distance below the atrial levels, the QRS resembles somewhat the QRS of one or more precordial leads and usually aV_F (figs. 1, 4, 5). These levels and the leads obtained from them are called *ventricular*. When the exploring electrode is 2.5 cm. below and in some cases also 5 cm. below the lowest atrial level, the recorded QRS complex is either intermediate between the QRS complexes in the atrial and ventricular leads (figs. 1, 4) or differs from these leads. When such QRS complexes are obtained the exploring electrode may be spoken of as being at a *transitional* level.

The transitional levels ranged between 40 and 50 cm. from the nares. In 28 cases there was a single transitional level at 42.5 cm. from the nares in 7 cases, at 45 cm. in 9, at 47.5 in 11 and at 50 cm. in 1. In 19 cases there were two transitional levels at 40 and 42.5 cm. in 2 cases, at 42.5 and 45 cm. in 11, at 45 and 47.5 cm. in 5 and at 47.5 and 50 cm. in 1. In 3 cases there were no transitional leads; in 2 of these the QRS complex in the lead from the level immediately below the lowest atrial level resembled a precordial QRS complex, and in the third case such a QRS complex was present at the lowest atrial level.

There was a ventricular level in every case at 52.5 cm., at 50 cm. in 48 cases, at 47.5 cm. in 32 cases, and at 45 cm. in 11 cases.

Anatomic location of the transitional and ventricular levels was attempted by means of the roentgenograms. The esophagus passes through the diaphragm at the level of the body of the tenth or eleventh thoracic vertebra.[33] In the roentgenograms the tube may be observed to curve more or less abruptly towards the left as it turns to enter the stomach (fig. 1). This change in direction is usually opposite the tenth or eleventh thoracic vertebra, in a few cases opposite the twelfth. In none of the 43 cases in which roentgenograms were available was there a ventricular level above the body of the tenth thoracic vertebra. In 19 cases the electrode position corresponding to the highest ventricular lead was opposite the body of the tenth thoracic vertebra. In the remaining 24 cases it was below or beyond, that is, opposite the body of the eleventh thoracic vertebra or lower, or somewhere on the tube after it had swung away from the spine towards the stomach. The highest ventricular level seemed to be located within the last few centimeters of the thoracic portion of the esophagus or definitely in the abdomen (fig. 1). Helm, Helm and Wolferth[20] found that when the exploring electrode was in the lowest 1½ inches of thoracic esophagus, the electrocardiograms resembled sometimes those of atrial levels, sometimes Lead II or a lead connecting left leg and spine of right scapula, and sometimes they were transitional. We believe our observations are in general agreement with the observations of these authors even though our indifferent electrode differed from theirs. Carlos Rubio[10] also found that when the exploring electrode was in the lowermost part of the thoracic esophagus as determined by fluoroscopy the electrocardiograms resembled either electrocardiograms from the atrial levels or the left leg lead. On the other hand, Nyboer[40] has diagramatically represented

a type case in which a considerable extent of ventricle above the diaphragm lies ventral to the esophagus, and in which the electrocardiogram from the supradiaphragmatic region is characteristic of the ventricular levels.

When the exploring electrode is in the stomach it is subject to motion and cannot be considered a fixed semidirect lead in the sense of the precordial leads or esophageal leads. In some locations in the stomach the electrode is more distant from the heart than when it lies

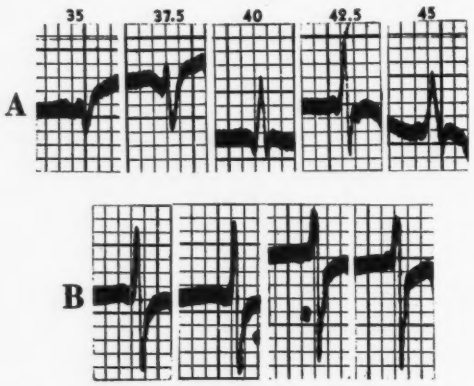

FIG. 3. P waves in atrial leads, enlarged. *A*, leads from different levels in one case. The small initial deflection preceding the main, large, diphasic part of P is negative in the 35, 37.5 and 40 cm. leads, diphasic in the 42.5 cm. lead and positive in the 45 cm. lead. *B*, successive P waves from a tracing (one omitted between the first and second complexes), showing respiratory variation of both the small initial part of P and the main diphasic part. The small initial deflection is negative in the first two complexes on the left, diphasic in the third complex and positive in the last one.

in the esophagus. The electrodes in the stomach are closest to the diaphragmatic surface of the heart.

Usually in a given case all ventricular leads recorded were similar to one another (figs 1, 4). In a few cases, however, there was a transition from higher levels to lower levels resembling the transition in leads from right to left across the chest (figs. 5, 7*A* and *B*). In figure 5, for example, the electrocardiogram from the 45 cm. level shows a small R and large S similar to Leads V_1 or V_2, whereas the electrocardiograms from the lower levels show predominantly a large R like Leads V_5 and V_6. It may be postulated in this case that the exploring electrode was over the right ventricle at 45 cm., but that the tube in the lower positions lay over the left ventricle. Further evidence was obtained for this inter-

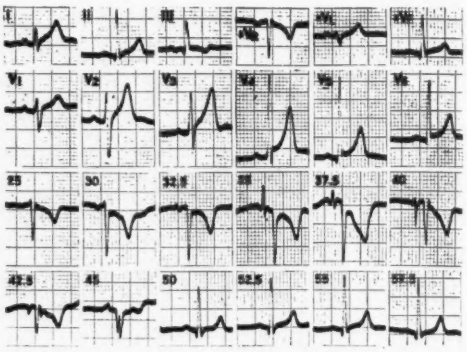

FIG. 4. Semivertical "electrocardiographic position." Absent (vestigial) R in lowest atrial leads (37.5, 40). Discussed in text.

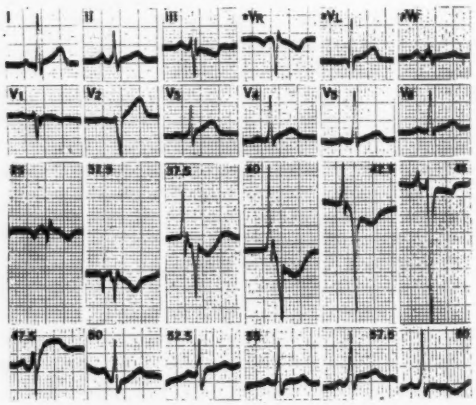

FIG. 5. Semihorizontal "electrocardiographic position." Absent R in lowest atrial lead (42.5). Transition from complex with small R and deep S (45) to complex with large R (50 to 60). Large P waves in atrial leads. Discussed in text.

pretation in this case by recording each esophageal and gastric lead simultaneously with both V_1 and V_5. From the earliest onset of QRS in any of the three leads to the onset of the intrinsic deflection was 0.02 sec. in the 45 cm. lead, 0.03 sec. in V_1 and 0.05 sec. in V_5. In the simultaneous records of the 55 cm. lead,

V_1 and V_5, the measurements were 0.05 sec., 0.03 sec., and 0.05 sec. respectively. The electrodes at 50 to 60 cm. from the nares were definitely in the stomach in this case, and the electrode at 47.5 cm. was either in the stomach or the abdominal portion of the esophagus. Such transitions may occur only with certain cardiac positions, but they at least indicate that an electrode in the lower part of the esophagus may occasionally be over the right ventricle in normal individuals.

The P Wave

In the supra-atrial leads P is low and inverted (figs. 1, 5), or, in two cases, diphasic. In the atrial leads the prominent part of P is a diphasic complex with rapid positive and negative deflections (figs. 1, 3, 4, 5), the downstroke representing the intrinsic deflection. Notching and slurring of P occurs in supra-atrial and atrial leads. In all cases in at least one of the atrial leads there is a small deflection immediately preceding the main diphasic part of the P wave (figs. 3 and 4, 35 and 37.5 cm.) which is most often inverted, sometimes upright, and occasionally diphasic (fig. 3). Hecht[19] described this deflection as uniformly positive. In the same individual this deflection may be negative in one atrial lead and positive in another (fig. 3*A*) with a tendency for the negative deflection to occur in the higher atrial leads and the positive deflection in the lower atrial leads. Occasionally respiratory variations occur (fig. 3*B*).

Table 1.—*Amplitude of P in Atrial Leads*

Amplitude = mv./10

Level	Small Initial Deflection				Main Diphasic Part of Complex				
	No. of Cases*	No. of Values†	Mean and S.D.	Range	No. of Cases	Positive Deflection		Negative Deflection	
						Mean and S.D.	Range	Mean and S.D.	Range
Highest atrial	43	46	-0.4 ± 0.3	$-1\frac{1}{2}$ to $+1$	50	2.2 ± 1.6	$\frac{1}{4}$ to 9	2.8 ± 1.5	$\frac{1}{4}$ to $6\frac{1}{4}$
Intermediate atrial	45	48	-0.2 ± 0.3	-1 to $+\frac{3}{4}$	48§	4.3 ± 2.2	1 to 12	2.6 ± 1.7	$\frac{1}{4}$ to $7\frac{1}{4}$
Lowest atrial	36	38	$+0.1 \pm 0.4$	$-\frac{3}{4}$ to $+1$	50	2.8 ± 1.5	$\frac{3}{4}$ to 7	1.9 ± 1.5¶	0 to $5\frac{3}{4}$¶
Level of largest positive deflection			(Not Recorded)		50	5.4 ± 3.2	2 to $23\frac{1}{4}$	(Not Recorded)	
Level of largest negative deflection			(Not Recorded)		50	(Not Recorded)		4.0 ± 1.8	1 to $9\frac{1}{2}$
Level of largest intrinsic deflection‡			(Not Recorded)		50	(Not Recorded)		9.9 ± 3.5	$5\frac{1}{4}$ to $27\frac{3}{4}$

* A small initial deflection was observed in at least one atrial lead in each case but not in all leads. The mean and S. D. were calculated for the cases in which the deflection occurred.

† In a number of the cases the deflection was diphasic, and both values were tabulated.

‡ The intrinsic deflection was measured from its onset (positive peak of P) to the lowest point below the baseline, unlike the other deflections which were measured as usual from the baseline.

§ In two cases there were only 2 atrial levels.

¶ Distribution skew. Other distributions in this table seemed approximately normal.

In the ventricular leads P is upright, low and rounded, similar to P in Lead II. In the transitional leads P sometimes resembles P in the ventricular leads, and sometimes it is intermediate between the P waves in the atrial and ventricular leads.

Table 1 summarizes the measurements of P. In a given case, in the atrial lead in which the largest positive deflection of P occurs, the probability of a positive deflection of at least 1.0 mv. is approximately 8 in 100; 1.3 mv., 1 in 100; 1.5 mv., 1 in 1000; and 2.0 mv., less than 1 in 10,000.

It has been stated that the ratio of negative to positive parts of the diphasic complex is larger in higher atrial leads than in lower atrial leads,[40, 48] but we did not find any relationship

TABLE 2.—*Amplitude of Q, R, and S*
Amplitude = mv./10

Level	Q or QS						R‡						S‡					
	No.*	No. with Q or QS	Percentile distribution† 10%	50% (Median)	90%	95%	Range	No.*	No. with R	Percentile distribution† 10%	50% (Median)	90%	95%	Range	No.*	No. with S	Percentile distribution† 10%	50% (Median)	90%	95%	Range
Supra-atrial, 5 cm. above highest atrial	50	44	0	9¼	15¾	18	0–19½	50	31	0	¼	1¾	4	0–5	49	8	0	0	5¼	11¾	0–16¼
Highest atrial	50	50	6¼	12	21	22	2¼–26¾	47	29	0	½	3¾	6	0–11	49	4	0	0	0	1¼	0–2
Intermediate atrial	48	48	7¼	14¼	21¼	29½	2–30	47	33	0	2	7¾	9	0–17	47	9	0	0	¼	¾	0–2¼
Lowest atrial	50	48	5¼	8	15	20	0–24½	50	44	0	12	25½	31¼	0–38	49	6	0	0	¼	1¼	0–35
Transitional§	47	46	2¼	4½	8¾	12	0–14¾	46	42	¼	8¾	22¾	27¼	0–32¾	46	21	0	0	4¼	8½	0–11
Ventricular	100	¶	0	¼	1½	1¾	0–2½	100	100	6	14¼	22	24½	1¾–30¾	95	¶	0	1	4½	5¼	0–8½

* Where the number is less than 50 it is either because an electrocardiogram was not available at the designated level or the electrocardiogram was unsatisfactory for measurement. Leads from two ventricular levels were measured in almost every case, the closest to and the furthest from the transitional level that were satisfactory for measurement.

† Here are recorded the upper limits of the lowest 10%, 50%, 90%, and 95% of values. Used in preference to mean and S.D. because some of the distributions were skew.

‡ R prime and S prime *not* included in the data. R prime occurred in the lead from the level 5 cm. above the highest atrial level in 5 cases (amplitudes = ½, 1, 1½, 1¾, and 1¾ mv./10), in one lowest atrial lead (amplitude = 4½ mv./10.) and in transitional leads of 5 cases (amplitudes = ¾, 1, 1¼, 1¼, and 8¼ mv./10). S prime occurred in transitional leads in 3 cases (amplitudes = 2¼, 4¾, and 11 mv./10).

§ The lead from the higher level when there were two transitional leads.

¶ Q present in both ventricular leads in 29 cases; absent in both in 16; present in the higher and absent in the lower in 3; absent in the higher and present in the lower in 2. S present in both ventricular leads in 24 cases; absent in both in 14; present in the upper and absent in the lower in 5; absent in the upper and present in the lower in 3; present in the upper, lower lead not available in 2; present in the lower, upper lead not available in 1.

of the ratio to levels. Our observations agree with the illustrations of Brown.[6]

The small initial deflection preceding the main diphasic part of P is of considerable interest. There is experimental evidence that coordinate contraction of the right atrium begins before that of the left.[2, 26] Brown[6] believed that a small deflection in atrial leads preceded the onset of P in simultaneously recorded Lead II by 0.011 to 0.018 sec., which he attributed to activity of the S-A node. Spühler[47] on the contrary found that the small initial deflection preceding the main diphasic part of P in the atrial leads did not precede the onset of P in Lead II, and he attributed the initial small deflection to right atrial activity. Our observations are in accord with those of Spühler.[47] In only 4 of our 50 subjects was the P-R interval in Lead II or V_1 shorter than in the atrial leads by more than 0.01 second, the limit of our measurement. In another group of 20 individuals with and without heart disease, in no instance did the onset of P in atrial esophageal leads precede that in simultaneously recorded Leads II and V_1.

The interval from the beginning of the small initial deflection of P to the beginning of the upstroke of the main diphasic part of the complex in the 50 normal subjects varied from 0.01 to 0.05 sec. (mean = 0.030 ± 0.010), an atrial lead with a definite small initial deflection being selected in each case for this measurement. This may possibly be an index of difference in onset of activation of parts of left and right atria. Spühler[47] found comparable values for this interval, an average of 0.02 to 0.04 second. Luisada[31, 32] found a significantly shorter interval of 0.01 to 0.02 second, but his technic differed from ours.

The interval from the beginning of P in the atrial leads to the onset of the intrinsic deflection represents approximately the time from the first recognizable atrial activity in the atrial leads to activation of myocardium closest to the electrode. An atrial lead in each case with a definite initial deflection preceding a large diphasic part of P was selected, and satisfactory tracings for measurement were obtained in 41 of the 50 cases. The range was from 0.03 to 0.08 second (mean = 0.056 ± 0.013). Hecht[19] gives an average value of 0.05 second for the interval in normal individuals from the onset of P in V_1 to the onset of the intrinsic deflection in the simultaneously recorded atrial esophageal leads.

The QRS Complex

General aspects of QRS are treated in this section, while other aspects are discussed in a subsequent section on electrocardiographic position. A summary of the measurements is presented in table 2.

In the supra-atrial leads QRS is predominately negative (figs. 1 and 4). In 48 of the 50 cases the negative part of the complex was largest; in the remaining 2 cases, a large late R exceeded the amplitude of the Q in the same supra-atrial lead. QRS in supra-atrial leads always resembled aV_R more than any other lead.

In the atrial leads there is a QS or QR complex, rarely a QRS complex. The deepest Q waves of the esophageal-gastric series appear here (table 2). An S wave occurs infrequently. The R wave when present usually increases in size from the upper atrial levels downward. The exceptions to this and other aspects of R in the supra-atrial and atrial leads are discussed in the section on electrocardiographic position.

The size of Q in electrocardiograms from levels below the atrium has been of considerable interest, because of the value of abnormal Q waves in the diagnosis of myocardial infarction. The data are summarized in tables 2 and 3. Nyboer[40] states that from levels 5 cm. or more below the lowest atrial level the Q wave is abnormal if it equals or exceeds 0.4 mv. or 20 per cent of the R in the same lead. Myers and Oren[34] state that a Q is abnormal if it equals or exceeds 0.4 mv. or 25 per cent of the R in the same lead in electrocardiograms from the levels, 45 to 55 cm. from the nares. There are 3 cases in this series which would be considered abnormal by Nyboer's criteria for absolute amplitude of the Q. The Q:R ratio in these 3 cases and in 12 additional cases would also be considered abnormal. The values for the leads from the level 7.5 cm. below the lowest atrial level fall well within the Nyboer limits. There are at least 16 cases in this series which would be con-

sidered abnormal by the criteria of Myers and Oren. In view of the somewhat variable location of the atrial levels it would seem undesirable to relate the Q to absolute levels in terms of distance from the nares. Nyboer's reference to the lowest atrial level seems more reasonable, but neither his criteria nor those of Myers and Oren for an abnormal Q in the esophageal and gastric leads seem adequate. The range of values given in tables 2 and 3 need not represent the full range of normal variation and larger Q waves may be expected to occur occasionally. In the lead from the level 7.5 cm. below the lowest atrial level Q was always considerably smaller in a given case than in the lead from the level 2.5 cm. below the lowest atrial level. With three exceptions Q was also smaller in the lead from the level 5 cm. below the lowest atrial level than in the lead from the level 2.5 cm. below the lowest atrial level.

Experimental studies and the analysis of human electrocardiograms led Lewis and Rothschild[27, 28] to conclude that the dorsal portion of the base of the left ventricle is activated late. Brown[6] confirmed this by measuring the time of onset of the intrinsic deflection after the beginning of QRS ("intrinsic interval") in leads obtained from the lower esophageal levels. Our observations agree. The intrinsic interval in our cases is definitely and consistently greatest in the lowest atrial and in the transitional leads in those cases in which there is an R following a Q in these leads and varies from 0.03 to 0.07 second (mean = 0.055 ± 0.008). The corresponding values are 0.02 to 0.06 second (mean = 0.038 ± 0.007) in the ventricular leads, 0.03 to 0.05 (mean = 0.040 ± 0.007) in V_5 and 0 to 0.03 (mean = 0.019 ± 0.006) in V_1. In only 4 of the 48 cases was the intrinsic interval as large in V_5 as in the lowest atrial or transitional leads, and in only 1 case was it larger. In only 1 of 48 cases was the interval as large in the ventricular leads as in the lowest atrial or transitional leads, and in only 1 case was it larger. In simultaneous tracings of 20 individuals with and without heart disease the onset of the intrinsic deflection in the lowest atrial and transitional leads in which there was an R following a Q occurred consistently from 0.01 to 0.04 second later than in V_5. The onset of the intrinsic deflection in the ventricular leads was usually practically simultaneous with that in V_5 although in some cases it was slightly later, and in 1 case slightly earlier.

In most of the 50 cases studied aV_F was very much like the ventricular leads (figs. 1 and 4)

TABLE 3.—*Amplitude of Q or QS and Q/R, Selected Levels*

Level	No. of Cases*	No. with Q or QS	Q or QS Amplitude = mv./10					Q/R				
			Percentile Distribution†				Range	Percentile Distribution†				Range
			10%	50% (Median)	90%	95%		10%	50% (Median)	90%	95%	
2.5 cm. below lowest atrial	47	46	2¼	4½	8¾	12	0–14¾	0.16	0.33	8.00	Infinity	0–infinity‡
5 cm. below lowest atrial	50	36	0	1	3	7	0–9	0	0.09	0.50	4.00	0–infinity‡
7.5 cm. below lowest atrial	43	24	0	¼	1½	1¾	0–2	0	0.02	0.10	0.15	0–0.30
45 cm. from nares	48	39	0	3	9	12½	0–12¾	0	0.30	1.50	28.00	0–infinity‡
47.5 cm. from nares	46	31	0	1	4	5¼	0–10½	0	0.07	0.62	0.92	0–infinity‡
50 cm. from nares	39	24	0	¾	1¾	1¾	0–4	0	0.04	0.20	0.25	0–0.30

* Where the number is less than 50 this is either because an electrocardiogram was not available at the designated level or because the electrocardiogram was unsatisfactory for measurement.

† Here are recorded the upper limits of the lowest 10%, 50%, 90%, and 95% of values. Used in preference to mean and S.D. because some of the distributions were skew.

‡ QS in 4 cases at 2.5 cm. below the lowest atrial level, in 1 case at 5 cm. below the lowest atrial level, in 2 cases at 45 cm., and in 1 case at 47.5 cm.

but in other cases there were differences. In figure 5, the small notched QRS complex in aV_F cannot be said to resemble closely the QRS of the ventricular leads. In figure 7*B* there are differences among the ventricular leads, and aV_F is more like the leads from the lowest levels (57.5 cm.). In figures 7*A*, 7*C* and 7*F* there is a good-sized S wave in the ventricular leads which is absent or very small in aV_F. In figures 7*D* and 7*E*, aV_F resembles the ventricular leads from the higher levels more than those in the lower levels. Compare the notching in aV_F and the 50 cm. lead in figure 7*D*, and the absence of S in aV_F and in the 45 and 47.5 cm. leads in figure 7*E*. Wilson, Johnston, Rosenbaum and Barker[56] also showed an electrocardiogram in which the left leg lead resembled leads from the higher ventricular levels more than those from the lower levels. Helm, Helm and Wolferth[20] found that gastric leads resembled Lead II or a lead connecting left leg and spine of right scapula with few exceptions. Carlos Rubio[10] found that aV_F and the ventricular leads only rarely differ to a significant degree.

What determines the variations in the relation of aV_F to the ventricular leads we do not know. If the potentials of the diaphragmatic surface of the heart are regularly transmitted to the left leg by way of selected adjacent structures and pathways then certain changes in position of the heart may account for the differences, but we have no evidence of the nature of these relations. The left leg is a "remote" electrode location in contrast to the "semidirect" locations in the esophagus and stomach. The predominant potentials contributing to the resultant recorded as aV_F may therefore be derived from a cardiac region more extensive than that which contributes to the ventricular leads, and under certain conditions the left leg electrode is more apt to be affected simultaneously by parts of the heart each giving rise to considerably different potentials, such as left and right ventricles, for example.

The T Wave and the RS-T Segment

Because of the difficulty of obtaining level baselines a quantitative evaluation of T amplitudes and RS-T deviations was not possible. In the supra-atrial and atrial leads the T waves were inverted with one possible exception in a lowest atrial lead. In transitional leads T was positive, negative or diphasic. In the ventricular leads, T was usually positive, although in a number of cases it was diphasic and in one case frankly negative. Of the 12 cases in which T was diphasic or negative in the ventricular leads, T was positive in aV_F in 5 and negative or diphasic in 7.

The amplitude of T ranged from slight inversion to approximately minus 0.8 mv. in the supra-atrial leads, from slight inversion to about minus 1.2 mv. (and one positive value) in the atrial leads, from minus 0.4 to plus 0.9 mv. in the transitional leads and from minus 0.25 to plus 0.95 mv. in the ventricular leads.

The origin of the RS-T segment (J) in the supra-atrial leads was depressed in all cases except one. In only a few cases was the depression more than 0.2 mv., and in none was it more than 0.3 mv. In one case there was RS-T elevation of less than 0.1 mv. In the atrial leads the origin of the RS-T segment was most frequently depressed, in a few cases as much as 0.4 mv. By contrast in a few cases there were elevations up to as much as 0.5 mv. Electropositive RS-T deviation in atrial leads similar in appearance and degree has been cited as evidence of atrial infarction.[14] In the transitional leads the origin of the RS-T segment deviation was most frequently within plus or minus 0.1 mv., but in a few cases depressions up to more than minus 0.5 mv., and elevations up to as much as plus 0.3 mv. were recorded. In the ventricular leads the origin of RS-T also was most frequently within plus or minus 0.1 mv. There were, however, a few cases of depression up to as much as minus 0.4 mv. and a few elevations up to as much as plus 0.4 mv.

Obvious distortions due to artefacts frequently occur in the region of the T wave and RS-T segment in many cases. These may recur regularly with each cardiac cycle and are possibly due to displacement of the electrode by the contracting heart. In answer to the question of whether the extreme deviations of the RS-T segment observed in some cases and the diphasic and inverted T waves of the ventricu-

lar leads may have a similar explanation, we can only say that such RS-T deviations and diphasic T waves occurred with fairly level baselines. The important practical observation is that diphasic T waves and extreme deviations of the RS-T segment may occur in the ventricular leads of normal individuals.

The "Electrocardiographic Position" of the Heart and the Esophageal and Gastric Leads

Wilson and his associates[54, 55] and Goldberger[17] attempted to correlate the patterns of the unipolar extremity leads with the position of the heart, and Gardberg and Ashman[15] did the same with the three standard limb leads. Carlos Rubio[10] and Myers and Klein[36] studied the esophageal and gastric electrocardiograms along with the unipolar extremity leads in relation to cardiac position; Carlos Rubio based his conclusions on six normal subjects and a number of patients with heart disease, and Myers and Klein illustrated what they consider to be type cases of cardiac position. Spühler[47] appreciated the significance of the relationship of the electrode at the lower esophageal levels to the position of the heart. Helm, Helm and Wolferth[20] found electrocardiograms from the transitional levels extremely variable and believed it was hopeless to set up normal standards for these levels, deviations from which might be clinically significant. This may be true, but if the variability is related to changes in cardiac position the study of these levels may have some value at least in this connection.

It should be stated at the outset that most of the recent discussion on the human electrocardiogram and cardiac position has been purely theoretic. Electrocardiograms have not been correlated with actual anatomic positions. This correlation is admittedly difficult, if not impossible, with available methods of study, particularly when relationships to multiple axes are involved, but the interpretations must therefore be regarded as tentative and subject to verification. This is exemplified in the use of the term "electrocardiographic position" by Wilson and his associates.[55]

The electrocardiograms of the 50 normal subjects were grouped into the categories "vertical," "semivertical," "intermediate," "semihorizontal" and "horizontal." The criteria of Wilson *et al.*[55] were used with the following reservations. Whereas these authors describe a "small" QRS complex in the left arm lead in the semivertical position and a "small" QRS complex in the left leg lead in the semihorizontal position, we required more specifically that these complexes consist of R and S and no Q. This was based on the significance attached to a Q in these leads by both Goldberger[17] and Myers and Klein.[36] By this classification there were 14 vertical, 7 semivertical, 3 intermediate, and 3 semihorizontal and horizontal cases. The remaining 18 of the electrocardiograms did not clearly fit any of these groups, or were intermediate in character between two of the groups. The small number in the semihorizontal-horizontal group is in agreement with the findings of Sokolow and Lyon[45] for normal adults. Because of the desirability of comparison with the vertical-semivertical groups, an additional group of 8 electrocardiograms was studied which fitted the semihorizontal-horizontal criteria. The latter were from subjects who did not fit the strict clinical standards set for the normal study for one reason or another, but whose standard limb leads, unipolar extremity leads and precordial leads were considered normal. These additional cases are considered only in this section on position and do not contribute to the data of other parts of this study. The anatomic position of the heart is referred to three axes, anteroposterior (ventrodorsal), longitudinal and transverse.[17, 36]

To determine whether the esophageal and gastric leads provided data that might support or negate some of the existing assumptions, it was accepted that if a described cardiac position called for the exploring electrode to be over right ventricle, the QRS of the derived lead should resemble the normal V_1 or V_2, showing a small R, deep S and an intrinsic interval up to and not exceeding 0.03 second. When the electrode position was over left ventricle the QRS of the derived lead should resemble the normal V_5 or V_6, showing a predominant R, and an intrinsic interval between 0.03 and 0.05 second. As the study developed

we observed that the size of a late R in the lowest atrial and/or transitional levels had a possible relationship to cardiac position.

We were unable to correlate either the qualitative appearance of the cardiac silhouette or a measurement in degrees of the long anatomic axis of the heart with the electrocardiographic position. We had hoped that the lateral roentgenograms might provide information on "forward" and "backward" rotation of the apex, but the detail of cardiac contour is often poor in these lateral roentgenograms, and besides we could not determine a satisfactory reference point for judging such rotation.

The Ventricular and Transitional Leads. In all the cases classified into the vertical and semivertical groups, the largest deflection of the QRS of the ventricular leads was an R with or without a small Q and S. That is, the ventricular leads resembled closely aV_F, V_5 and V_6. This is what might be expected since the electrode in the stomach or near the posterior attachment of diaphragm should be facing the epicardium of the left ventricle. The intrinsic interval in the ventricular leads in all the vertical and semivertical cases was 0.03 to 0.05 second. In the transitional leads it was as large or larger. These intrinsic intervals are consistent with the described positions. The transitional leads of the vertical group showed QR complexes, which is consistent with the described position, this complex being intermediate between the QRS of the atrial leads, and the QRS with predominant R from leads over the left ventricle. In the semivertical group 5 of the 7 cases also had QR complexes in the transitional leads. In one case, however, there was a W-shaped QS complex. This case is discussed further on as possibly indicative of forward rotation of the apex. In still another semivertical case there was a polyphasic QRS complex in the transitional lead.

In 8 of the 11 semihorizontal and horizontal cases the ventricular leads showed a small R and deep S, or both a small R and S, or a larger R approximately equal to the S in size. This is consistent with the described position of right ventricle or the posterior interventricular sulcus. In one of the normal semihorizontal cases and in one of the other semihorizontal cases there was a transition in the ventricular leads from a complex with a small R and deep S to one with a large R and small S as in leads from right to left across the precordium (fig. 5). In 2 of the cases a small Q preceded the R in some of the ventricular leads. In 3 of the cases there were QS complexes in transitional leads. In 2 of the cases there was a direct change going downward, from an atrial lead to a lead with a small R and deep S without an intervening transitional lead. The latter change was observed also in one intermediate case, but in none of the vertical or semivertical cases and suggests that the transition of electrode positions was from atrium to right ventricle. This should be a more likely transition in the described intermediate and horizontal-semihorizontal positions than in the vertical-semivertical positions. In one case a W-shaped complex entirely below the baseline persisted in all the ventricular leads, and it was questionable whether a tiny upward deflection preceded the W. This was one of the added horizontal cases that did not comply with the strict normal criteria, but there was no evidence of heart disease and no history that could be interpreted as previous angina pectoris or myocardial infarction.

In 7 of the 11 cases of the horizontal-semihorizontal group there was some transitional or ventricular lead with an intrinsic interval less than 0.03 second, which is consistent with an electrode position over right ventricle. In 2 of the cases the shortest intrinsic interval in transitional or ventricular leads was 0.03 second while in another case it was 0.04 second. In one case an intrinsic interval could not be measured since there was a QS in all the ventricular leads. In some of the cases showing a short intrinsic interval this occurred at the higher ventricular levels, whereas lower ventricular levels showed an intrinsic interval of 0.04 second.

In the intermediate group QRS in the ventricular leads was characterized by a predominant R, which is consistent with the described position.

The Late R in the Lowest Atrial and Transitional Leads. In the electrocardiograms from the lowest atrial or transitional levels in the

vertical and semivertical groups there was a tendency to a large R (fig. 1, table 4). In 11 of the 21 cases R was larger here than in any other lead of the same subject including the precordial leads. This was not so in any of the intermediate, horizontal or semihorizontal cases. The amplitude of the late R (R following Q) was measured in each case in the lowest atrial lead and in leads from levels 2.5 cm. above and below the lowest atrial lead. The highest R of these three leads was tabulated for each case, and the comparison by groups is shown in table 4. In view of the variability of absolute amplitudes of electrocardiograms of different individuals we also determined the ratio of this R to the highest R of the precordial leads in the same subject.

TABLE 4.—*Relation of Electrocardiographic Position to Amplitude of Largest Late R (R Following Q) Among Lowest Atrial Lead and Leads from Levels 2.5 Cm. Above and Below Lowest Atrial Level*

Electrocardiographic Position	No. of Cases	No. with Late R	Amplitude = mv./10		Ratio to Largest Precordial R	
			Mean and S.D.	Range	Mean and S.D.	Range
Vertical	14	14	22.0 ± 8.9	4¾ to 38*	1.24 ± 0.56	0.24 to 2.20†
Semivertical	7	6	17.7 ± 9.9	0 to 32¾	1.05 ± 0.95	0 to 2.77
Intermediate	8	8	9.9 ± 4.9	3 to 16½	0.52 ± 0.25	0.14 to 0.91
Semihorizontal and horizontal	11	9	6.5 ± 5.9	0 to 19¾	0.36 ± 0.13	0 to 0.70‡

* The amplitude in one case is unknown since the R went off the tracing, but it was greater than 32.

† The ratio in one case is unknown since the R went off the tracing, but it was greater than 1.39.

‡ The ratio in one semihorizontal case is unknown since the precordial R went off the tracing, but it was less than one.

It is not possible to be sure of the nature of the distributions in these small groups, although only the amplitudes of R in the semihorizontal-horizontal group suggested a possible skew distribution, whereas the other distributions could be normal. Applying the statistical tests for normal distributions, the differences in the amplitudes of R are statistically highly significant between the vertical and intermediate groups and between the vertical and horizontal-semihorizontal groups. There is no statistically significant difference in amplitude of R between any other two of the groups. The ratios of the esophageal R to precordial R suggest similar differences, but statistical tests were not applied. Of the 21 in the vertical and semivertical groups there were 11 instances with a lower atrial or transitional R larger than 2.0 mv., while in no instance among the 19 intermediate, semihorizontal and horizontal cases was there an R of this amplitude. R was smaller than 1.5 mv. in 17 of the intermediate, horizontal and semihorizontal cases, whereas it was so small in only 6 of the vertical and semivertical cases.

The tendency to a large R in the lower atrial or transitional leads in the vertical and semivertical groups is consistent with the position of an electrode close to the dorsal portion of the left ventricle. The base of the left ventricle might be expected to lie in close apposition with the lower thoracic portion of the esophagus when the heart is vertical and rotated clockwise. It might be expected from the anatomic relations that an electrode in the lower thoracic part of the esophagus would often be closer to the left ventricle than when situated on the precordium or in the stomach.

The possible relation to cardiac position of the large R in the lower atrial and transitional leads focussed our attention on 7 cases in this normal series in which a late R was completely absent or very small. These cases included 1 with a semivertical position (fig. 4), 1 with a semihorizontal position (fig. 5), 1 with a horizontal position and 4 other cases not classified in the original grouping. If the absence of the R or a small R is related to cardiac position it may be postulated that it would occur when the dorsal basal part of left ventricle loses its close relationship to the lower thoracic end of the esophagus. We would expect this to occur with extreme forward rotation of the apex, extreme counterclockwise rotation, and possibly extreme rotation into the horizontal pos-

tion. Evidence for these possibilities may be presented by correlation with the other leads, although there is, of course, no independent proof for the interpretations.

Figure 4 represents the electrocardiograms from the case with a semivertical position. Here the vestigial R in the lowest atrial and transitional leads could be explained by forward rotation of the apex. In this position the left ventricle could still lie on the diaphragm and produce the potentials in the ventricular leads and aV_F, and the region of the anterior interventricular sulcus could still face the left shoulder and produce the potentials of aV_L. It should be noted that aV_F does not have the diphasic or inverted T in this case that has been postulated with forward rotation of the apex.[17, 36] This case cannot be distinguished from the other cases with semivertical position in this series on the basis of the unipolar extremity leads. There were 5 cases of this series in which the predominant part of QRS in aV_F was R and in which T was diphasic or negative in aV_F, the signs postulated by Goldberger[17] and Myers and Klein[36] as possibly indicative of forward rotation. In 1 of these 5 cases R was absent in the lowest atrial level and in another it was rather small, whereas in the remaining 3 cases it was large. There is thus no consistent association between the signs given by Goldberger and Myers and Klein as possibly indicative of forward rotation and an absent or small late R in the lower atrial and transitional leads.

The electrocardiogram in figure 5 may represent counterclockwise and/or semihorizontal rotation and shows the transition in the ventricular leads from a complex with small R and large S to a complex with predominantly large R.

The Late R in the Right Arm Lead and in the Supra-atrial Leads. Both Goldberger[17] and Myers, Klein, and Stofer[35, 36] have interpreted the late R in aV_R (R following Q or S) as arising from the dorsal portion of the base of the left ventricle when this region of the heart is turned toward the right arm. According to Goldberger[17] the latter occurs in extreme clockwise rotation of the heart or backward rotation of the apex in which case there is a late R also in the esophageal leads.

A number of observations in the cases we studied forced us to examine these assumptions further. A relatively large late R may be present in electrocardiograms from the supra-atrial levels and higher atrial levels and still be absent in the lower atrial levels (fig. 5). If the late R is derived only from the dorsal basal portion of the left ventricle and is due to backward rotation of the apex or clockwise rotation of the heart, it seemed to us that this R should be larger in electrocardiograms from the lower esophageal levels where the dorsal portion of the base of the left ventricle is closer to the esophagus than in leads from higher levels. In figure 1 this is true, but in figure 5 this is not so. The late R in the supra-atrial leads and probably also aV_R of figure 5 must have some other origin. On the other hand, in some of the cases with hearts in the vertical and semivertical position, in which there were large late R waves in the lower atrial and transitional leads, the late R in aV_R and in the supra-atrial leads was absent or insignificant (fig. 1).

Both Goldberger[17] and Myers and Klein[36] agree that clockwise rotation is more apt to be associated with the vertical position than with the horizontal position. Yet there is no evidence from our data that either the incidence of the late R in aV_R, or the amplitude, is greater in the vertical than in the semihorizontal-horizontal groups. On the basis of the chi square test the incidence of the late R, regardless of amplitude, is greater in the vertical group than in the intermediate group, the difference being statistically significant, and it is greater in the horizontal group than in the intermediate group, the difference being statistically highly significant. There is no statistical difference between any other two of the groups. As regards amplitudes, most of the distributions were definitely skew, and the usually applied tests for normal distributions were not used. Simple inspection of the data shows no evidence that the amplitudes are greater in the vertical than in the semihorizontal-horizontal groups.

Myers and Klein[36] studied the electrocardiographic patterns in leads from successive positions across the back and front of the chest

leading towards the right arm and showed that a late R could be traced across the back of the chest, but not across the front. To compare the right arm lead with the chest leads (fig. 6) we used V_R, V leads for the chest positions and one and one-half times the usual standardization. In figure 6*A* is an electrocardiogram which

The fact that late R waves appeared in aV_R more frequently either in the vertical or horizontal cases than in the intermediate cases suggests the possibility that the late R in aV_R tends to appear when the cardiac position deviates either way from the intermediate position. We might expect different explanations

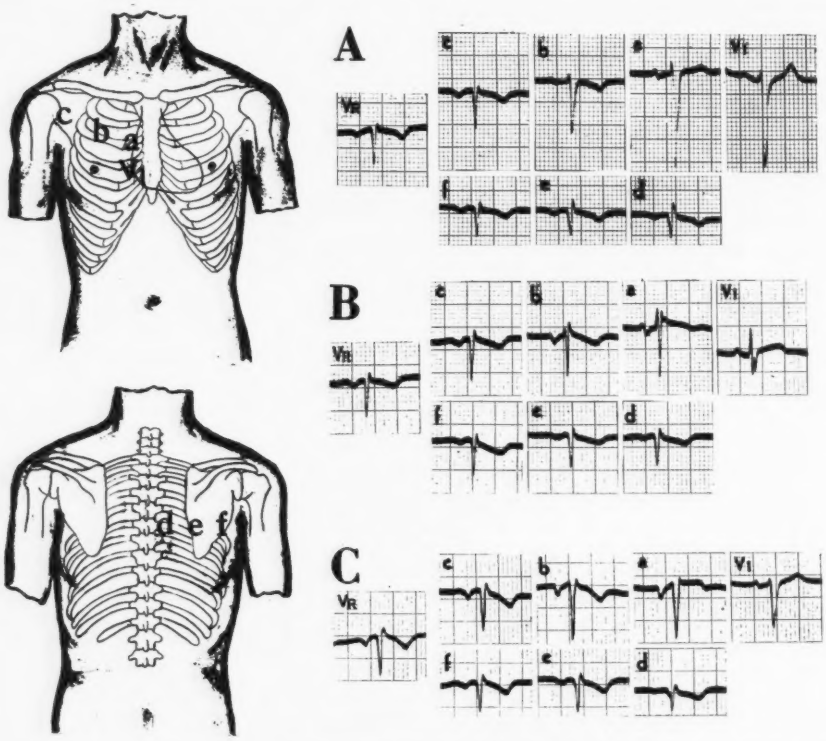

FIG. 6. Origin of late R in V_R. Transmission of potentials across front and back of chest. *a*, *b*, *c*, *d*, *e*, *f*, exploring electrode positions for electrocardiograms with corresponding designations. These electrocardiograms and V_R recorded at 1.5 normal standardization (1.0 mv. = 15 mm.) with Wilson terminal as indifferent electrode (*not* "augmented" unipolar leads). *A*, No late R across front of chest, late R across back of chest. *B*, *C*, Equally prominent late R across front and back of chest.

agrees with the observation of Myers and Klein. In figures 6*B* and 6*C*, however, from 2 of the normal cases in which there was a late R in the right arm lead and in the supra-atrial leads but no R in the lowest atrial leads, leads from the anterior chest positions show as prominent a late R as do those from the posterior chest positions. It is, therefore, apparent that the explanation given for the late R in aV_R[17, 35, 36] does not hold for all cases.

for its appearance with opposite directional changes from a midposition. In a study of intracardiac leads Kossmann and associates[23] recorded a large late positive deflection of QRS at the base of the right ventricle, which they believe may originate in the crista supraventricularis of the right ventricle, which may be transmitted to surface leads, and which may be simultaneous with a late R in V_R. We believe that counterclockwise rotation of the

heart would be one factor favoring the transmission of this potential to the right arm; this might be one explanation of the late R in aV_R in our cases in which there was no late R in the lowest esophageal leads.

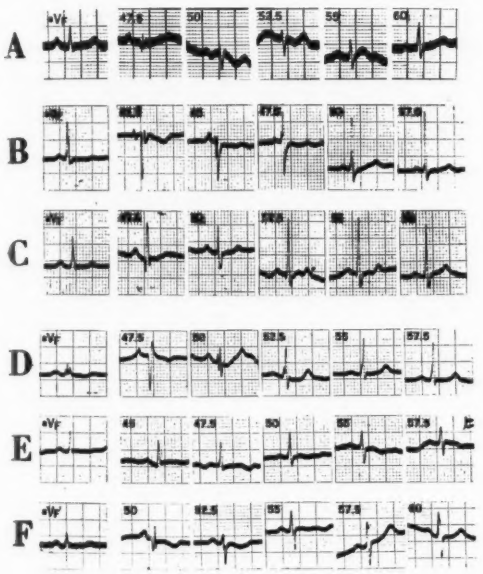

FIG. 7. Comparisons of aV_F and ventricular leads. *A*, *B*, *C* are from the 50 normal subjects. *D*, *E*, *F* are from other cases. In *A*, *C*, *F* there is a deep S in ventricular leads which is absent in aV_F. In *B* there are differences among ventricular leads, and aV_F is more like leads from lower levels (57.5 cm.). In *D* and *E*, aV_F is more like leads from higher ventricular levels, aV_F in *D* more like the 50 cm. lead, and aV_F in *E*, like the 45 and 47.5 cm. leads.

RS Complexes in Precordial Leads. Goldberger[17] has postulated that RS complexes (Q absent) are obtained in precordial leads when the exploring electrode faces the epicardial surface of the right ventricle. Some of the electrocardiograms illustrated by Goldberger show a rather large R in proportion to the S. When such complexes are obtained in V_5 and V_6 this author has postulated extreme clockwise rotation.

In this series there were 6 cases in which there was an R and S of variable size and no Q in V_5 and V_6. One each of these cases was from the vertical, the intermediate, the semihorizontal and horizontal groups. Two were from among the additional semihorizontal and horizontal cases that did not fit the original normal criteria. While the esophageal leads are consistent with the Goldberger interpretation in 3 of the cases, they are inconsistent in the other 3.

If Goldberger is correct we should not expect leads from the lower part of the esophagus in these cases to show RS complexes. For in extreme clockwise rotation the right ventricle should not be in relation to the lower part of the esophagus. In the 2 cases with hearts in the vertical and the intermediate positions and in one case with the heart in the semihorizontal position QR or QRS complexes were obtained from the lower esophageal levels. In the case showing the vertical position, furthermore, the R in leads from the lowest atrial and transitional levels was quite large as was the late R in aV_R and the supra-atrial leads.

One of the cases showing the semihorizontal and 2 showing the horizontal positions, however, were not consistent with the Goldberger interpretation. In figure 5 is illustrated one of these cases, and leads from the lower esophagus and stomach show RS complexes as well as the precordial leads. One would have to postulate the right ventricle facing not only all 6 standard precordial positions but the lower esophagus and stomach as well to be consistent with the Goldberger hypothesis.

Our conclusion is that RS complexes in precordial leads are not recorded exclusively when the exploring electrode faces the epicardial surface of right ventricle. We believe that the small Q may normally be absent in leads obtained with the precordial electrode facing the epicardium of left ventricle.

Cases in Which There is a Small QRS with Proportionately Large Q or QS in aV_L. There were 18 cases which did not fit exactly into the preliminary classification already described. Of these there were 12 cases characterized by a small QRS complex in aV_L with a definite Q or QS; the Q though small was a sizeable proportion of the QRS complex. Both Goldberger[17] and Myers and Klein[36] have described QR complexes in aV_L and explained them as derived

from potentials from the "back of the heart." Goldberger attributed the presence of a large Q and R in aV_L to backward rotation of the apex. Myers and Klein agree to this interpretation when Q is less than 25 per cent of the R, but they believe that a large Q and small R appear in aV_L when there is some counterclockwise rotation in the vertical position. There were only 2 of the 50 cases which clearly fit these descriptions and in which the size of the QRS in aV_L compared with those illustrated by these authors.

In the 12 other cases which are the subject of this section, the QRS was much smaller and it did not appear justifiable to apply an arbitrary Q:R ratio in dealing with such small complexes. Some of these cases seemed to fit well into the semivertical group and might have been so classified by some authors. In fact, in the electrocardiograms of one of the patients who was studied at two different times, aV_L showed at one time a small R and S and no Q, whereas at another time a definite Q was present which was proportionately large compared to the size of the QRS. Even the latter electrocardiograms showed respiratory variation, however, so that the Q disappeared in occasional complexes. In 4 of these cases the characteristics of aV_F, and of the various esophageal and gastric leads were consistent with the criteria for the vertical-semivertical groups. On present evidence, therefore, there is nothing inconsistent with the interpretation that these are cases of semi-vertical position with some backward rotation. Three other cases were among those in which there was an absent R in the lowest atrial and transitional leads and in the remaining 5 cases there was a complex with small R and large S in passing from the atrial to the ventricular leads. These 8 cases may be consistent with counterclockwise rotation, but it seems to us they are consistent with backward rotation only if associated with a certain degree of counterclockwise or/and horizontal rotation.

Summary and Conclusions

1. The esophageal and gastric electrocardiograms of 50 men without clinical evidence of heart disease are described, and various quantitative data are presented. The positions of the electrodes are correlated with roentgenograms.

2. Electrocardiographic evidence is presented to show that the electrode in the lower end of the esophagus may occasionally lie over the right ventricle.

3. Previous observations are confirmed that a P wave with an intrinsic deflection is obtained in esophageal leads when the exploring electrode lies over the left atrium. The position of the atrial levels tends to vary with the heights of individuals, but the variation is considerably less than the heights. An atrial level was obtained at 40 cm. from the nares in all but one case, at 37.5 and 40 cm. in all but 3, and at 35 to 40 cm. inclusive in 34 of the 50 cases. The electrode positions from which ventricular leads are obtained are in the lowest few centimeters of the thoracic esophagus or in the stomach.

4. The P wave in the atrial levels is characterized by a small initial deflection followed by a larger diphasic deflection. From the onset of the former to the onset of the latter may represent an index of difference in time of activation of parts of right and left atria. In normal subjects the interval is from 0.01 to 0.05 sec. (mean = 0.03 sec. $\pm$ 0.01). From the onset of the small initial deflection to the onset of the intrinsic deflection of P the interval is from 0.03 to 0.08 sec. (mean = 0.056 $\pm$ 0.013). There is no evidence of atrial activation in esophageal leads that precedes the earliest signs of atrial activation in Leads II and V_1.

5. The existing criteria for the size of the normal Q in transitional and ventricular leads are inadequate and may lead to false diagnoses of abnormality. Data on the Q wave in these 50 normal subjects are presented. By measurements of the time of onset of intrinsic deflections previous observations are confirmed that the base of the left ventricle is a region of late activation. The QRS of the ventricular leads usually resembles aV_F, but there are important exceptions.

6. The T wave in ventricular leads is usually positive, but it may be diphasic or inverted in normal subjects. Extreme RS-T deviations may occur normally in esophageal and gastric leads.

7. The esophageal and gastric leads support

some of the assumptions regarding the "electrocardiographic position" of the heart based on the unipolar extremity leads and precordial leads, but they are inconsistent with other assumptions. In general the ventricular leads are what would be expected from the described positions. A large, late R occurs in the lowest atrial and transitional leads in subjects showing vertical and semivertical positions, and this is consistent with the described position. Absence of late R or small late R in the lowest atrial and transitional leads is possibly due to (a) forward rotation of the apex, (b) extreme counterclockwise rotation, (c) extreme horizontal rotation. The explanations of Goldberger and Myers and Klein for the origin of the late R in aV_R are analyzed; it is concluded that in addition to being derived from the posterior basal portion of the left ventricle, as postulated by these authors, a late R in aV_R may have other origins. The Goldberger theory that RS complexes (no Q wave) in precordial leads are derived from electrode positions over the right ventricle only is contradicted. It was not possible to correlate the "electrocardiographic position" with the cardiac contour in anteroposterior or lateral roentgenograms obtained with the subject supine or with a measurement in degrees of the long axis of the heart.

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RS-T Segment Displacement in Induced Coronary Insufficiency as Studied with Esophageal Leads

By LEONARD SCHERLIS, M.D., AVERY A. SANDBERG, M.D., JOSEPH WENER, M.D., ARTHUR M. MASTER, M.D., AND ARTHUR GRISHMAN, M.D.

Esophageal electrocardiograms are utilized as a means of studying the left ventricular cavity potentials in induced coronary insufficiency in patients with angina pectoris. Depressions of the RS-T segment recorded in precordial leads after exercise were consistently associated with simultaneously recorded RS-T elevations at the atrial level. These RS-T deviations are interpreted as indicating that in coronary insufficiency there are widespread changes involving the subendocardial aspect of the left ventricle. A circuit is described to enable the recording of better technical esophageal records despite interference due to extraneous low frequency potentials.

THE CHARACTERISTIC precordial electrocardiographic findings of acute coronary insufficiency consist of depression of the RS-T segment and flattening or inversion of the T waves.[1] Autopsy studies have at times demonstrated subendocardial necrosis or infarction to be present in the myocardium of patients who had such an electrocardiographic pattern for varying periods prior to death.[1-3]

The depressions of the RS-T segments after exercise[1] and after the breathing of 10 per cent oxygen[4] in patients with coronary sclerosis have been ascribed to anoxemia of the subendocardium. Numerous experiments involving the production of injury to the subendocardial surface of the left ventricle have resulted in elevation of the RS-T segments in leads recorded within the left ventricle[5-8] and depression of the RS-T segment in epicardial leads recorded directly over the damaged areas.[5-9]

Esophageal electrocardiograms recorded at the atrial levels have been shown to reflect left ventricular cavity potentials.[10] Leads taken below this level usually record the potentials of the posterior and diaphragmatic surfaces of the left ventricle.

In this study, esophageal leads were used to investigate the nature of the RS-T segment displacement in induced coronary insufficiency.[11] If the RS-T depression in the precordial leads is due to subendocardial changes, positive displacement of the RS-T segment should be recorded in those esophageal leads reflecting predominantly left ventricular cavity potentials.

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METHODS

The patients selected for this study had definite histories of angina pectoris and on prior occasions had positive responses after two-step exercise tests.[12] In no patient was there a history or electrocardiographic evidence of a previous myocardial infarction. No patient had received digitalis for several months prior to this study. Following the recording of control electrocardiograms, including standard, Wilson unipolar extremity and precordial leads,[13] and unipolar esophageal electrocardiograms, the patients performed the two-step exercise test with the electrodes still in place. Immediately upon the completion of the exercise and at frequent intervals thereafter, electrocardiograms were secured, the first esophageal lead being recorded within thirty seconds. To diminish the elapsed time in recording as many leads as possible, an instomatic control and external multiple-selector switch box were utilized.

The esophageal electrode employed in this study consists of an ordinary rubber tube containing a central core of 15 wires, each separately connected to external metal bands 1.75 cm. apart. This tube was introduced into the nasal cavity of the patient, and advanced until the tip, by fluoroscopic control, was selectively located 4 to 5 cm. below the diaphragm. Prior to exercise, esophageal electrocardiograms were recorded at each of the 15 levels repre-

ented by the metal bands. Simultaneously, two other electrocardiograms were recorded, usually V_1 and V_5 being selected.

After exercise the esophageal lead at that atrial level which in the control best represented left ventricular cavity potential was recorded. In addition, the esophageal lead reflecting the posterior or diaphragmatic surface of the heart was taken when conditions permitted. The amplitude of the individual tracings could be selectively varied by sensitivity controls, and these were utilized to allow maximum amplitude at all levels within the limits of respiratory excursions. The response to 1 mv. introduced into the circuit has been employed to permit comparison of the records taken at varying sensitivities, and this is recorded in each figure.

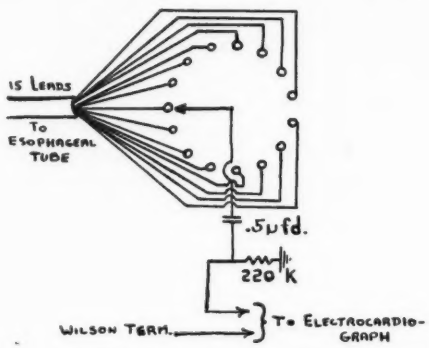

FIG. 1. Electrical filter unit of the Technicon three channel cardiograph.

Esophageal electrocardiograms may be markedly distorted, or their recording made difficult, because of low frequency gastric, esophageal, and diaphragmatic potentials. These extraneous influences may at times be so pronounced as to make any detailed analysis of atrial and particularly ventricular complexes erroneous. In this study, a condenser-resistor arrangement was inserted between the electrode and the amplifier input (fig. 1). The condenser and resistor were so selected as to attentuate all frequencies of 1.5 cycles per second and less, while having negligible effect (5 per cent or less) on frequencies of more than 2.5 cycles per second.[14] This device made it possible to obtain consistently adequate records at any esophageal level both before and after exercise. At the onset of this study, records were obtained with and without the presence of the filter in the circuit, and were found to be similar in detail and timing.

The electrocardiograph used throughout this study was a three channel direct writing Technicon Cardiograph. All records were inscribed at usual speed and double the normal speed to permit better analysis and timing.

Results

Nine patients with angina pectoris performed the exercise test after control records had been obtained. Three of these patients had essentially normal records prior to exercise. In the remaining 6 cases, the resting records revealed diphasic to inverted T waves in the precordial and standard leads with slight depression of the RS-T segment. Immediately after exercise depression of the RS-T segment in the precordial leads (V_4 or V_5) was regularly associated with simultaneous elevation of the RS-T segment in the esophageal lead at the atrial level reflecting left ventricular cavity potentials (fig. 2). In each of the patients who, prior to exercise, demonstrated RS-T depressions precordially and minimal RS-T elevation at the atrial level showed a marked increase after exercise in the depression precordially and in the elevations recorded at the atrial level (fig. 3).

In three instances, significant depressions of the RS-T segments in the esophageal leads reflecting the posterior or diaphragmatic surface of the ventricle were recorded after exercise (fig. 4).

Inversion or flattening of the T waves in the precordial leads after exercise was usually associated with similar findings in the esophageal leads reflecting the posterior or diaphragmatic surface of the left ventricle. The T waves recorded at the atrial level were generally negative before exercise and became diphasic or positive following exercise. All electrocardiograms returned to the resting records within fifteen minutes.

Six control individuals with normal electrocardiograms, normal physical examination and no history of cardiac disturbance demonstrated no change in the precordial or esophageal leads after exercise.

Discussion

The above observations indicate that RS-T segment depressions recorded in induced coronary insufficiency in the precordial leads and in the esophageal leads reflecting the posterior or diaphragmatic ventricular surface are regularly associated with RS-T segment elevations

in the esophageal leads reflecting left ventricular cavity potential.

diograms at the atrial level reflect left ventricular cavity potentials. Brown[10] noted that "if

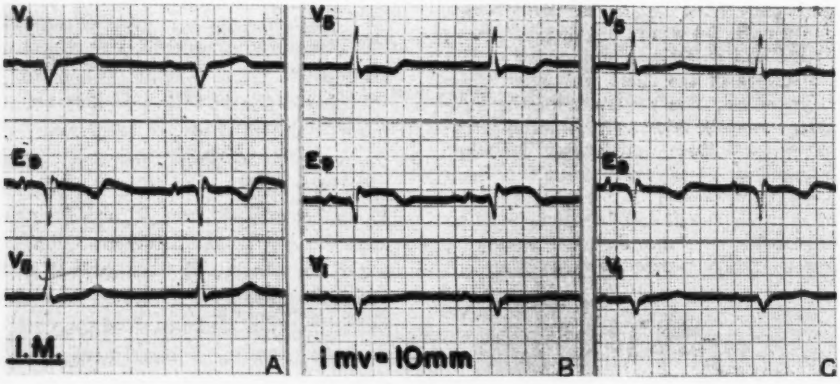

FIG. 2. I. M.: 68 year old white man. Angina pectoris for six years. Resting standard and precordial leads normal. (In this and the following figures, the three leads were taken simultaneously and have been separated and remounted in the interest of saving space.) *A*. Resting control record. E_9: Esophageal record taken at atrial level. Note intrinsic atrial deflection, Qr ventricular deflection, and isoelectric RS-T segment. *B*. Immediately after exercise. RS-T depressed in V_5 and elevated in E_9. *C*: Ten minutes after exercise. Record has returned to resting state

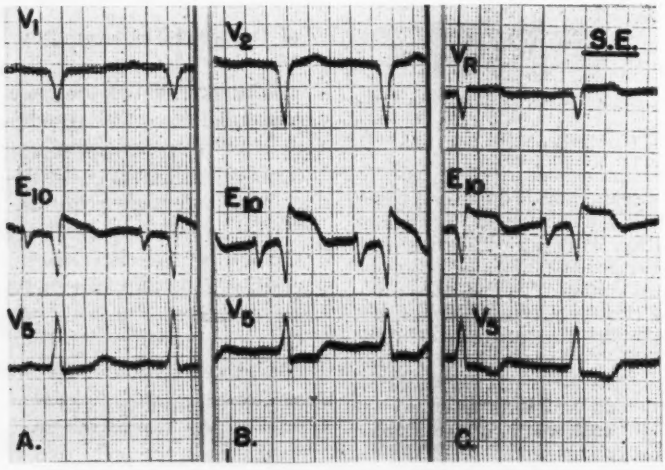

FIG. 3. S. E.: 38 year old white man. Severe angina pectoris for one and one-half years. Resting standard and precordial leads not remarkable except for minimal depression of RS-T segment in Leads V_5 and V_6. *A*. Resting control record. E_{10}: Esophageal record taken at atrial level; RS-T elevated prior to exercise. V_5: RS-T slightly depressed. *B*. Immediately after exercise. E_{10}: RS-T markedly elevated. V_5: RS-T more depressed than in *A*. *C*. Five minutes after exercise. Changes less marked than in *B*. RS-T slightly elevated in V_R.

The interpretation of the RS-T deviations as obtained in this study is dependent upon the demonstration that esophageal electrocar-

an exploring electrode is placed against, o almost against, auricular musculature, then a the onset of the ventricular excitation it i

tapping the electropotential changes occurring in the ventricle under peculiar circumstances. It is connected to the internal surface of the ventricle by an electrolytic medium: the wall of the auricle and the auricular contents."

Esophageal patterns at the atrial level are essentially similar to those obtained by electrodes within the left ventricular cavity in animals.[15, 16] Other investigators[6, 17-19] have been in general agreement that esophageal leads at the atrial level reflect essentially left ventricular cavity potential. The patterns obtained at the atrial level were those of a QS or Q wave followed by a small R. Sodi-Pallares[32] in a study of left heart catheterization in human subjects has found that the normal potential inside the left ventricular cavity is QS in configuration. This would further corroborate the fact that the potentials obtained at the atrial level reflect left ventricular cavity potentials.

Esophageal electrocardiograms recorded from the lower part of the esophagus usually reflect the potentials of the posterior surface of the left ventricle.[10] Application of this fact has been made in the diagnosis of posterior myocardial infarctions.[17, 20-22]

In the actual selection of the control endocardial lead from the fifteen esophageal leads recorded, the most important criterion employed was the presence of a QS or Qr pattern with the initial inscription of the Q wave in the esophageal lead preceding or coinciding with the inscription of the initial ventricular deflection in V_1 and V_5. The tracing containing this complex usually revealed an intrinsic deflection of the P wave, but that the presence of such an intrinsic deflection is no constant criterion of endocardiac potential was pointed out by Burchell[20] who stated that ". . . Q and QR deflections characteristic of atrial levels may sometimes persist below the level where the P waves no longer show intrinsic deflections." Thus, the RS-T deviations in the electrocardiogram recorded at the atrial level are believed to be essentially similar to those recorded inside the left ventricle, while those at the lower esophageal levels reflect the potentials of the posterior and diaphragmatic surface of the left ventricle.

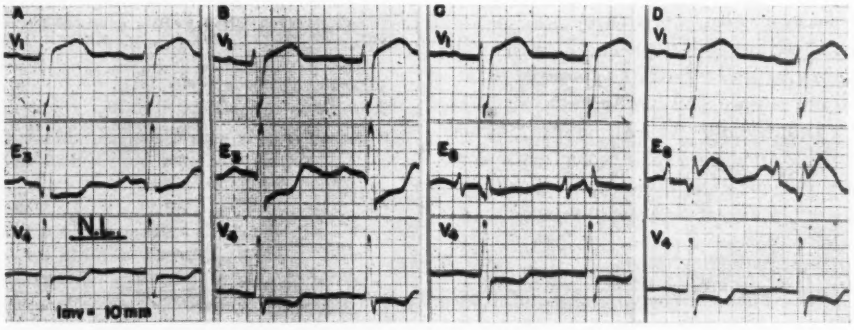

FIG. 4. N. L.: 56 year old white man. Angina pectoris for two years. Resting standard and precordial leads reveal minimal depression of RS-T segments in Leads I, II, V_4, V_5 and V_6; T diphasic in V_4, V_5 and V_6. (All records taken at twice normal speed.) *A*. Resting control record. E_3: Esophageal record taken at posterior surface, left ventricle. RS-T depressed prior to exercise in E_3 and V_4. *B*. Immediately after exercise. Increased RS-T depression in E_3 and V_4. *C*. Resting control record E_8: Esophageal record taken at atrial level. RS-T isoelectric. *D*. Immediately after exercise. RS-T markedly elevated in E_8 and depressed in V_4.

The significance of RS-T deviations has been the subject of many experimental studies. Experiments in animals have shown that damage to the epicardial surface produces positive displacement of the RS-T segment in epicardial leads and negative displacement in leads from the cardiac cavity.[5-8] Trauma to the subendocardial surface, however, produced negative displacement over the circumscribed epicardial surface,[9] and positive displacement in the car-

diac cavity.[5-8] Evidence in support of subendocardial damage giving rise to negative deviations of the RS-T segment in precordial leads is also derived from isolated cases of subendocardial infarction[23, 24] and the finding of subendocardial necrosis in acute coronary insufficiency.[1, 2] During intracardiac catheterization, contact of the electrode with the endocardium of the right or left ventricle can cause upward deviation of the RS-T segments in intracardiac leads.[25-27] The failure of simultaneously recorded precordial leads to reveal RS-T deviations of either direction was usually interpreted as meaning that the extent of the injury must be very localized in distribution.

Under those circumstances in which the unipolar right arm lead reflects the potential variations of the endocardial surfaces and cavities of the two ventricles[28, 29] elevation of the RS-T segment in V_R has been reported in acute coronary insufficiency[30] and in the induced hypoxemia test for coronary insufficiency.[4] Similar results were obtained in this study. The elevations were interpreted as reflecting positivity of the ventricular cavity. A similar explanation has been given for the precordial elevation of the RS-T segment after hypoxemia tests in two patients with previous anterior wall infarction, the left ventricular cavity potential being tapped through the myocardial window.[4]

The positive RS-T segment deviation at the atrial level recorded simultaneously with depressions of the RS-T segment in precordial and lower esophageal levels, as secured in this study, signifies widespread involvement of the subendocardium of the left ventricle.

In accord with the present concepts of the theory of the current of injury[4, 8, 15, 31] the results of this study would indicate that in induced coronary insufficiency there is predominant injury to the subendocardium.

Summary

1. The results of this study indicate that RS-T segment depressions recorded in induced coronary insufficiency in the precordial leads and in the esophageal leads reflecting posterior or diaphragmatic ventricular surface are regularly associated with RS-T segment elevations in the esophageal leads reflecting left ventricular cavity potential.

2. These observations strongly suggest that the electrocardiographic changes in coronary insufficiency are due to widespread involvement of the subendocardial aspect of the myocardium

3. A circuit is described to minimize the interference due to excursion of the base line in esophageal electrocardiography.

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A-V Conduction in Auricular Flutter

By M. Besoain-Santander, M.D., A. Pick, M.D. and R. Langendorf, M.D.

Flutter of the auricles may be associated with either a regular or an irregular ventricular rate. The former occurs as a rule in the untreated patient, the latter as a result of digitalis therapy. An attempt was made to explain the irregular ventricular response in auricular flutter as a result of a conduction disturbance similar to that seen in sinus rhythm with second degree A-V block characterized by progressive lengthening of the A-V conduction time preceding the dropped beat (Wenckebach phenomenon). Such an approach was suggested by the peculiar arrangement of the ventricular beats in some cases of auricular flutter. Similarly, in order to account for certain features of the arrhythmia it was assumed that some of the non-conducted flutter impulses penetrate into the A-V junction and thus influence the conduction of the subsequent flutter impulses.

IN AURICULAR flutter, the tissues of the A-V junction are exposed to impulses occurring in rapid succession, the rate of which greatly exceeds that of normal sinus impulses. Our understanding of the protective function of the A-V junction which reduces the number of such rapid impulses conveyed to the ventricles to a rate more economical for the heart, is based on the classical studies of Lewis[1] on the law of the heart. However, only a few attempts have been made[2–5] to analyze the complex mechanism of the conduction disturbance which develops in the A-V junction with rapid stimulation such as occurs in auricular flutter. It would appear that A-V conduction during auricular flutter follows some definite rules rather than being simply a matter of chance. A study of auricular flutter was, therefore, undertaken both in cases with regular A-V conduction and those with clinical ventricular arrhythmia due to apparently irregular A-V block.

The observations were made on 27 patients, 14 male and 13 female, between the ages of 21 and 90. The clinical diagnosis was hypertensive and/or arteriosclerotic heart disease in 22 cases and rheumatic heart disease in the remaining 5 cases. Fifty-nine records were obtained during auricular flutter and additional records were available for comparison in 17 cases before the onset or after the termination of the auricular flutter.

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A-V Conduction in Untreated Cases of Auricular Flutter

In table 1 the type of A-V conduction in the first record with auricular flutter is listed. Six cases were already under medication, 21 were untreated at the time. Prior to treatment, the prevalent finding was a regular 2:1 A-V ratio (47.6 per cent). In 19 per cent, a basic 2:1 conduction was found with occasional changes to 1:1 or 4:1 A-V conduction. In most cases, both with regular and irregular conduction, the

Table 1.—*Type of A-V Conduction in the First Tracing Obtained During Auricular Flutter*

A-V conduction	Untreated Cases	Cases already under treatment
Regular		
1:1 conduction	1 (4.8%)	1
2:1 conduction	10 (47.6%)	
Irregular		
with basic 2:1 conduction	4 (19%)	2
with alternation of 2:1 and 4:1 conduction	1 (4.8%)	
Totally irregular		
with ventricular rate over 100	2 (9.5%)	1
with ventricular rate below 80	3 (14.3%)	2
Total	21	6

ventricular rate was over 100 per minute. In 3 untreated cases it was below 80. These were patients in the older age group with evidence of arteriosclerotic heart disease. Two of them showed the pattern of right bundle branch system block and one, in addition, showed signs of a remote myocardial infarct. It appeared that in these cases an A-V conduction defect became apparent with the onset of the rapid auricular rate.[6] Persistent 1:1 A-V conduction was seen in two cases. The first, reported elsewhere,[7] appeared to be paroxysmal in origin and the underlying mechanism became obvious only under carotid sinus pressure, producing a transient 2:1 A-V conduction. In the other instance, 1:1 A-V conduction was seen for a short time after conversion of auricular fibrillation to flutter by quinidine. The single case of table 1 showing alternating 2:1 and 4:1 conduction will be discussed later (see fig. 4B).

The Different Types of A-V Conduction in the Entire Group of Cases

As shown in table 2, our cases can be divided into (a) cases with regular ventricular action due to a constant A-V ratio and fixed relation of QRS complexes to a preceding F wave and (b) cases with irregular ventricular action, due to varying A-V conduction, characterized by a changing relation of QRS to the preceding F wave. A fixed F-R distance was assumed if the QRS complex appeared consistently at identical points on the flutter waves. In cases of complete A-V block a regular ventricular rate occurs with changing F-R distances. Transitions between groups (a) and (b) were seen, as in fig. 1, in which a rhythmic ventricular action with a constant F-R distance was occasionally interrupted by an irregular ventricular response.

(*a*) *Fixed F-R Relation.* A constant F-R interval would be expected in these cases; however, as is the rule in auricular flutter, the determination of exact values of the A-V conduction time (F-R interval) is difficult, for two reasons: first, the point on a flutter wave at which the impulse begins to travel towards the ventricles cannot be established[2, 5]; therefore, measurements of A-V conduction represent only approximate and relative values. For the sake of simplicity, this point in all of our records was assumed to coincide with the beginning of the ascending part of an F wave. As long as our criteria of the "beginning" of an F wave remain the same our conclusions based on relative values of A-V conduction remain valid. The other difficulty consists in the determination of which of the flutter waves, preceding a QRS, is conducted. Usually F waves are seen to coincide partially with a QRS complex and it seems improbable[5, 6] that such an F wave is transmitted, since the distance (0.07–0.14 sec.) from its "beginning" to the onset of QRS appears too short. The alternative, prolonged A-V conduction of one of the preceding F waves, seems more likely.

TABLE 2.—*Different Types of A-V Conduction in the Entire Series of Tracings*

A-V Conduction	Number of Tracings
a) *Fixed F-R relation*	
Regular conduction in a 1:1 ratio ratio	2 (3.4%)
Regular conduction in a 2:1 ratio	21 (35.6%)
Regular conduction in a 4:1 ratio	3 ((5.1%)
b) *Changing F-R relation*	
Irregular conduction in a basic 2:1 ratio	12 (20.3%)
Irregular conduction in a basic 4:1 ratio	4 (6.8%)
Regular conduction in a 3:1 ratio	2 (3.4%)
Alternation of a 2:1 and 3:1 ratio	1 (1.7%)
Alternation of a 2:1 and 4:1 ratio*	5 (8.5%)
Alternation of a 4:1 and 6:1 ratio	1 (1.7%)
Almost complete A-V block	1 (1.7%)
Irregular conduction, no basic A-V ratio established	7 (11.8%)
Total	59

* Alternative explanation (3:1 conduction with alternation of F-R intervals) discussed in text.

A 2:1 A-V ratio was found to be the most common type of A-V conduction (35.6 per cent) in all analyzed tracings. For reasons given above, the time of A-V conduction was assumed to be 0.26 to 0.46 second. Similarly, in our cases of regular 4:1 conduction, the conduction time varied between 0.33 and 0.43 second assuming that A-V conduction is from the last completed

F wave preceding a QRS. If one assumes that conduction is from the second last completed F wave preceding QRS, the respective values in our cases would be 0.45 to 0.78 second.

Such marked delay of A-V conduction as compared with P-R intervals during sinus rhythm is found regularly in auricular flutter even if the ventricular rate is within the range seen in sinus tachycardia or normal sinus rhythm. To our knowledge, Wenckebach and Winterberg were the first[5] to explain the long duration of the F-R interval by assuming some penetration into the A-V junction of the preceding auricular impulse. The non-conducted F impulses, by shortening the time for recovery in that portion of the junctional tissues into which they penetrate, are responsible for the prolongation of the A-V conduction time of the subsequent flutter impulse. Further details of such concealed conduction[8] in the A-V junction, as indicated in all of our diagrams, will be discussed later in connection with irregular conduction of auricular flutter waves.

Two cases with an apparently constant 3:1 ratio of auricular to ventricular activation showed a slight alternation of F-R distances varying between 0.35 and 0.41 second (or 0.57–0.65 sec. respectively), and were, therefore, listed in table 2 under group b. Conditions seemed to be present comparable with those discussed below in connection with figure 3A and B.

(*b*) *Variable F-R Relation.* Except in the presence of complete A-V block, these cases are associated with a more or less marked arrhythmia of the ventricles. This irregularity may be complete, similar to that seen in auricular fibrillation, or there may be an allorhythmic repetition of certain groups, or a fundamentally rhythmic action of the ventricles may be disturbed only occasionally by some irregularity. One such case is shown in fig. 1. A regular 2:1 A-V ratio, manifested by a regular sequence of QRS complexes with fixed F-R distances is disturbed in two instances. For reasons discussed above, the A-V conduction time of the regular beats is assumed to be 0.35 to 0.36 second. The eleventh QRS appears prematurely (R-R 0.32 sec.), 0.46 second after the onset of the last preceding completed F wave. Its slightly different contour may be explained by superposition of the following F wave and/or by aberrant intraventricular conduction due to its premature occurrence. The next (twelfth) beat is also premature (R-R 0.36 sec.), its F-R distance being 0.38 second. It initiates another series of regular 2:1 A-V conduction, but it will be seen that those F waves blocked in the first part of the record are now conducted, and vice versa. The occurrence of this single instance of transitory 1:1 conduction seems to confirm the assumption of partial (concealed) conduction of apparently non-conducted F waves during

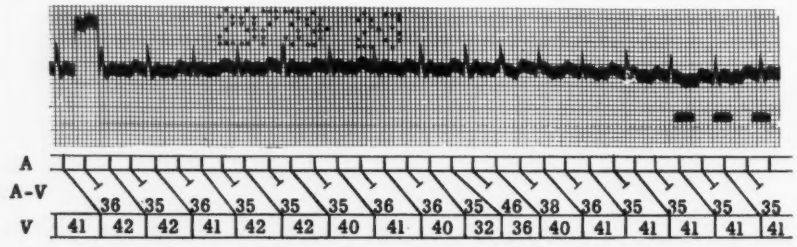

FIG. 1. The conventions in the diagram below this and the following records are those used customarily. A-V represents the spread of a flutter impulse through the A-V junction between the auricles (A) and the ventricles (V). Oblique lines at different angles indicate varying speed of impulse conduction through the A-V junction; the short lines at right angles to the oblique lines, blockage of the impulse. Varying lengths of oblique lines, representing blocked impulses indicate the varying distance to which the impulse penetrates into the A-V junction.

Lead III: Auricular flutter with regular 2:1 A-V conduction, disturbed by a single instance (eleventh QRS) of 1:1 conduction. Discussed in text.

regular 2:1 conduction, as indicated in the diagram of fig. 1. The different F-R intervals bear an inverse relationship to the respective R-F distances, reflecting the incomplete recovery in the A-V junction, which is also responsible for the prolongation of the A-V conduction time during the part of the record with regular ventricular rate. In figure 2A a marked ventricular irregularity is seen. Most of the R-R intervals are slightly longer than two F-F intervals. The shorter R-R intervals tend to show progressive shortening preceding a long interval and the longer R-R intervals measure less than two short ones. Thus, the ventricular arrhythmia resembles that produced by a second degree A-V block of the Wenckebach type. Furthermore, as seen in typical Wenckebach periods, the R-R interval following the ventricular pause is found to be longer than that preceding the pause. To explain the whole mechanism of A-V conduction, it is assumed that all flutter impulses penetrate some distance into the upper part of the A-V conduction system and that only every second one is transmitted to the lower portion. Thus, a functional and constant A-V block high in the node reduced by half the number of auricular impulses crossing the A-V junction and another lower region of delayed conduction produced the progressive type of A-V block with (single) dropped beats.

In all records listed in table 2 as irregular, with a basic 2:1 or 4:1 A-V conduction, it was possible to establish an explanation similar to that shown for figure 2A. Another example is shown in figure 2B, where the long R-R cycles are more frequent. Again it can be seen that these long R-R intervals are both shorter than the sum of two short R-R or four F-F intervals, while the short R-R cycles are longer than two F-F intervals. The assumed conditions of A-V conduction and the twofold block is shown diagrammatically below the tracing.

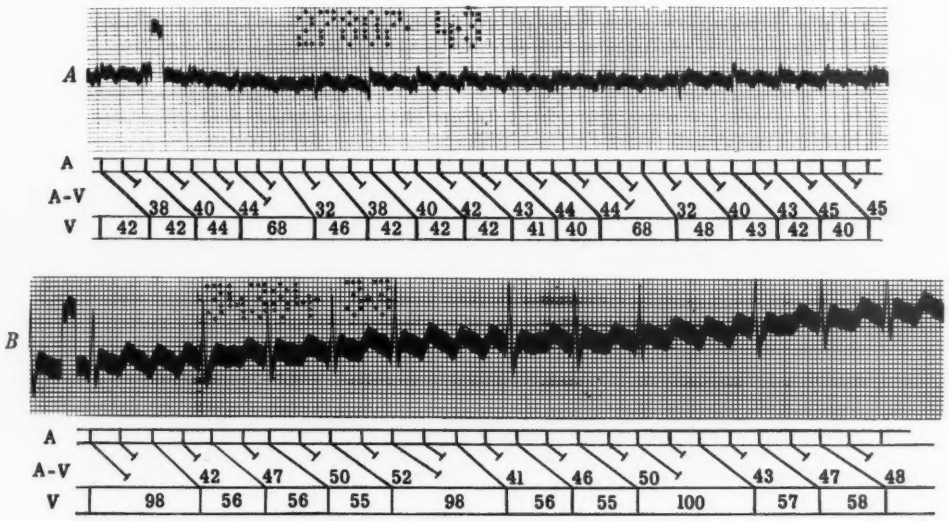

FIG. 2. Conventions as in figure 1. Wenckebach periods during auricular flutter. Discussed in text. (*A*) Lead III: Dropped beat following seven successive transmissions of 2:1 auricular flutter with progressive lengthening of the F-R intervals of conducted beats. (*B*) Lead III: Dropped beat following four and three successive transmissions of 2:1 auricular flutter with progressive lengthening of the F-R intervals of subsequent conducted beats.

In some cases, the lower area of block gives rise to regularly recurring dropped beats, so that ventricular allorhythmia is produced (fig. 3A–D). Figure 3A represents a case of ventricular "bigeminy" during auricular flutter. Short intervals (0.74–0.75 sec.) alternate with

longer ones (0.80–0.81 sec.). The short R-R distances are longer than two F-F intervals, the longer R-R are shorter than four F-F intervals. Here, a 3:2 block of the Wenckebach type in the lower part of the A-V junction is assumed to be paired with a regular 2:1 response in the upper part. Penetration of apparently blocked flutter impulses into the latter region is indicated in the diagram to explain the prolonged A-V conduction time after relatively long ventricular intervals. However, since the sum of two consecutive R-R intervals

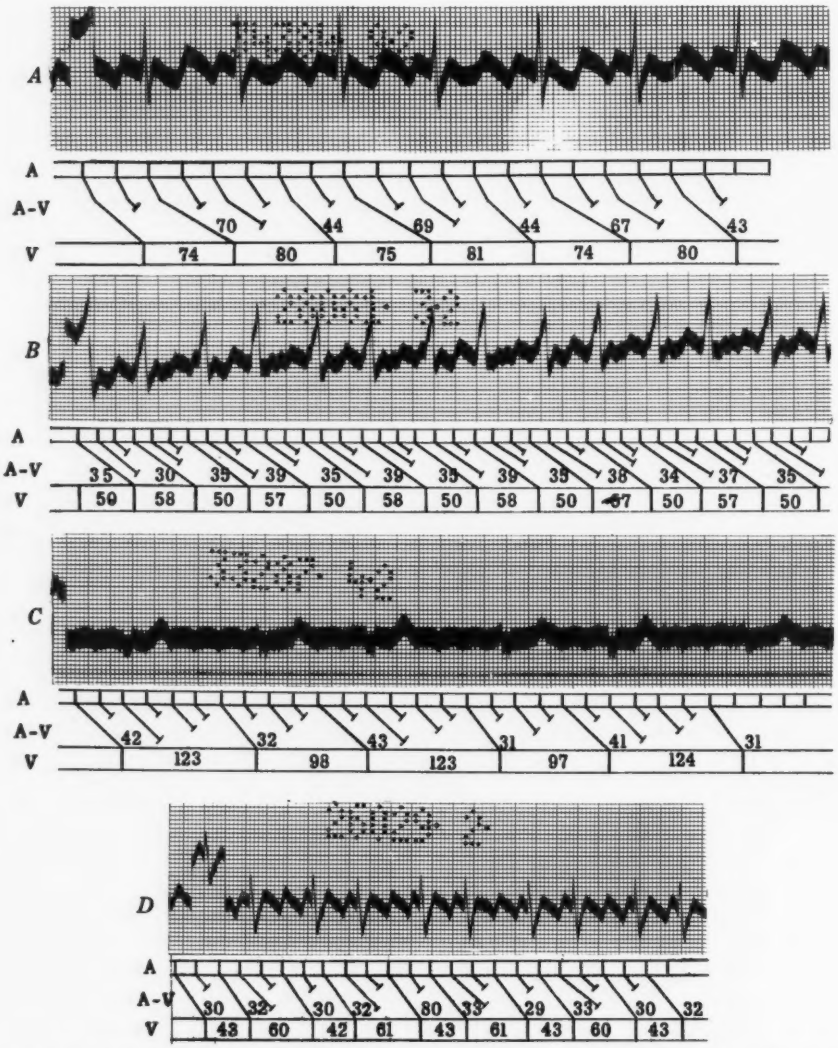

FIG. 3. Conventions as in figure 1. "Ventricular bigeminy" during auricular flutter. Note varying extent of penetration of non-conducted auricular impulses. Discussed in text. Compare with figures 6 and 7. (*A*) Lead II: 2:1 alternating with 4:1 A-V conduction. (*B*) Lead II: regular 3:1 A-V conduction with alternation of the F-R intervals of the conducted beats. (*C*) Lead II: 4:1 alternating with 6:1 A-V conduction. (*D*) Lead II: 2:1 alternating with 3:1 A-V conduction.

equals six F-F intervals, an alternative explanation, namely regular 3:1 block has to be considered and is shown below in an analogous case (fig. 3B). On this last assumption, a more complicated mechanism involving different degrees of penetration of blocked auricular impulses has to be postulated to account for alternation of the length of the F-R intervals.[4] Such varying penetration could be expected to occur because of the varying cycle length preceding each attempt at conduction. Whereas this uneven (3:1) conduction ratio could not be excluded in two cases listed as such in table 2, it appeared less likely in others such as the case shown in figure 3A. In this patient the flutter attack started with a regular 2:1 conduction and, under treatment with digitalis, more and more instances of 4:1 conduction appeared until the latter ratio was finally established. The tracing of figure 3A was obtained during an intermediate period.

In figure 3C the basic mechanism is similar, but the degree of delay in A-V conduction is greater. The long R-R intervals (1.23–1.24 sec.) are shorter than six F-F intervals and the short R-R (0.97–0.98 sec.) longer than four F-F intervals. The total sum of a short plus a succeeding long interval equals ten F-F intervals. If we again assume a double region of block, every second auricular impulse would be blocked at the upper level and, of the remaining ones, alternately every second, then every third, would reach the ventricles. A detailed analysis of the tracing seems to confirm this assumption. It can be seen that following the first conducted impulse with a conduction time (F-R interval) of 0.42 second full conduction is not re-established with an R-F distance of 0.44 second (R-F distance of the fourth F wave) and only the sixth F wave (R-F distance 0.88 sec.) is transmitted to the ventricles with an F-R interval of 0.32 second. Due to the marked shortening of the latter, the following fourth F wave now occurs 0.54 second after a QRS, this interval permitting a ventricular response at an F-R interval of 0.43 second. Although these figures seem to be in close accordance with the fundamental laws of recovery and conduction, it should be realized that they represent only relative and average values—changes of the refractory period as a result of concealed A-V conduction are not taken into consideration. As will be discussed later, the true state of recovery does not appear to be identical at all levels of the A-V junction since the penetration of non-conducted flutter impulses is expected to be more or less inversely proportional to the preceding cycle length (fig. 6). It would appear that such a mechanism plays its part in the production of alternating 4:1 and 6:1 conduction in this case.

A somewhat different mechanism seemed to produce the allorhythmia present in tracing 3D. There too, an alternation of long and short R-R intervals is seen and the sum of two such consecutive R-R intervals equals five F-F intervals. This is the only case of our series where no other explanation than alternation of 2:1 and 3:1 A-V conduction could be established. The prolonged A-V conduction time of 0.30 second after an R-R interval of 0.60 second may be the consequence of concealed conduction of preceding auricular impulses. The failure of every second F wave following the QRS with the longer conduction time to be transmitted to the ventricles could be explained, as was figure 3C, either by a shortened recovery time or by a different degree of A-V penetration by the blocked flutter impulses. The latter is assumed in the diagram to this figure.

Alternation of the A-V conduction time, giving rise to ventricular bigeminy as presented in figure 3A–D, was seen in 9 of our cases. This allorhythmia was persistent throughout two of the records and disturbed by some other irregularity in the others.

In figure 4 there is illustrated a case listed in table 2 as almost complete A-V block. The auricular flutter rate is 260, the ventricular rate in Lead III is 52 with slight variations of R-R distances not exceeding 0.03 second. The peristent variations of F-R distances with a regular rate of both auricles and ventricles suggest the presence of complete A-V block and an idioventricular rhythm in these leads. However, in Lead V_2, a single ventricular beat appearing prematurely (ventricular capture) interrupts the regular ventricular action.

Finally, in 11.8 per cent of the records (table

2) we were unable to find a definite and consistent relationship of auricular and ventricular activation. If in such cases the ventricular rate is slow and irregular and the F-R intervals vary throughout the record, one could consider the possibility of complete A-V block above the nodal pacemaker and a second degree A-V block with the Wenckebach phenomenon below it. Analogous cases with multiple regions of block in the A-V junction in the presence of auricular fibrillation have been reported from this department.[9] The failure of a satisfactory analysis in some cases is, however, not surprising in view of the complexity of the factors, which determine conduction of flutter impulses viz. concealed conduction with different degree of penetration and the ensuing variations of the duration of refractory period and recovery time at different levels of the A-V junction.

A-V Conduction and Ventricular Premature Beats

In 6 of our records premature ventricular complexes of apparently ectopic origin were seen and their interference with A-V conduction of flutter impulses could be studied.

In figure 5A a basic 2:1 A-V conduction with an F-R interval of 0.32 second is present. A ventricular premature beat interferes with the conduction of an F wave in the lower part of the A-V junction, but apparently not with the concealed conduction of the succeeding F wave, since the F-R interval following the compensatory pause remains prolonged (0.3) sec.).

In figures 5B and 5C, tracings of another case are shown taken on different days. The patient was treated with digitalis and a regular F-R ratio of 4:1 was established. In both tracings a premature beat occurring relatively late in diastole did not produce a "compensatory pause." Two possible explanations are indicated in the diagrams. In figure 5B the premature beat is considered to be of ectopic ventricular origin and interfering with A-V conduction. The prolongation of the subsequent F-R interval may be ascribed either to retrograde conduction of the premature beat or to the shorter R-F distance of the conducted flutter wave. This prolonged F-R distance, following the premature complex is not seen in figure 5C. An alternative explanation viz. transient 3:2 block in the lower part of

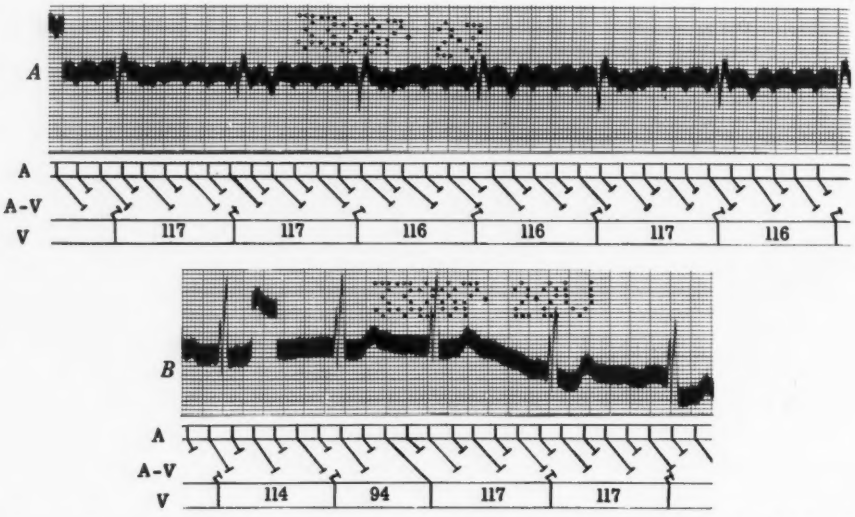

FIG. 4. Conventions as in figure 1. Auricular flutter with complete A-V block in Lead III and a single "ventricular capture" in Lead V_2. Discussed in text.

the A-V junction with aberrant intraventricular conduction of the second flutter impulse, seems more adequate and is so indicated in the diagram.

become apparent with auricular impulses occurring in rapid succession. Again, in cases of auricular flutter and complete A-V block, this block may disappear with the onset of sinus

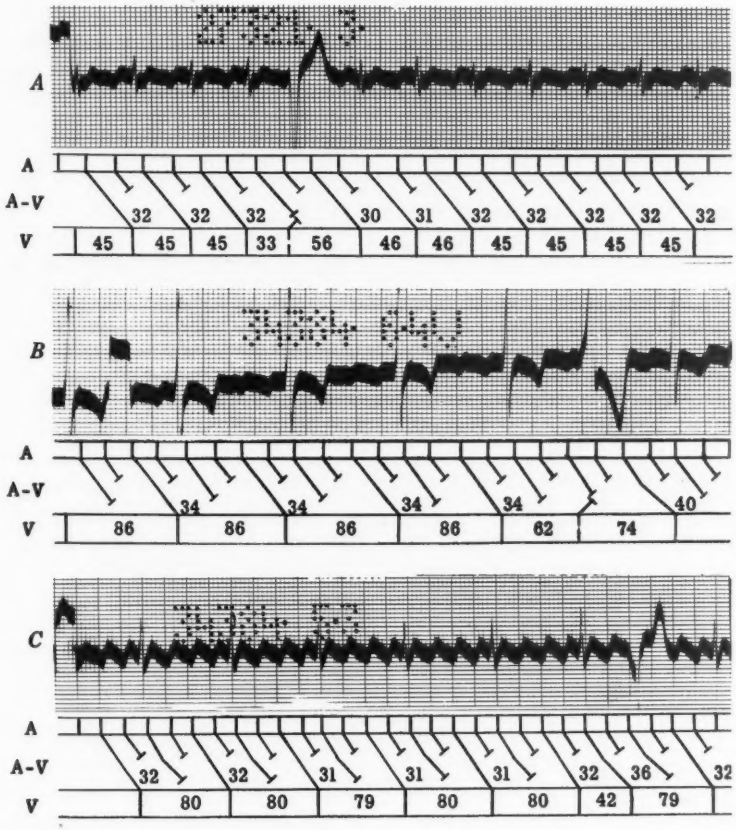

FIG. 5. Conventions as in figure 1. In addition, broken lines indicate aberrant conduction within the ventricles. Ventricular premature beats during auricular flutter. Discussed in text. (*A*) Lead III and (*B*) Lead V_4: Bizarre ventricular complex of ectopic origin. (*C*) Lead III: Bizarre ventricular complex due to aberrant intraventricular conduction of a transmitted flutter impulse.

COMMENT

Our analysis of tracings of auricular flutter has been based on the fundamental laws valid for A-V conduction during sinus rhythm.[2] However, some differences are to be expected in view of the rapid rate of auricular impulses and the longer refractory period of the A-V junction compared with that of the auricular muscle.[1] Thus, a latent conduction defect may

rhythm.[10] The more effective action of digitalis on A-V conduction in auricular flutter and fibrillation may be explained in a similar way.

The usual A-V conduction found at the onset of auricular flutter is 2:1.[6] This condition is a manifestation of interference with transmission due to the fact that the refractory period of the A-V junction is normally longer than the F-F interval. 1:1 conduction occurs only exceptionally. It may be the consequence

of a relatively slow flutter rate of the auricles due to quinidine or of an abbreviation of the recovery time of A-V conduction such as seen in children or after exercise or emotion.

In our material it was found that cases with an initial 2:1 ventricular response in auricular flutter had, during sinus rhythm, a P-R interval of from 0.12 to 0.18 second. On the other hand, cases with first and second degree A-V block during sinus rhythm developed 4:1 block or Wenckebach periods with the onset of auricular flutter. It would, therefore, appear that a ratio of A-V conduction greater than 2:1 in auricular flutter can be considered as the first sign of a disturbance of A-V conduction, corresponding to P-R prolongation during sinus rhythm. However, sometimes the A-V conduction defect may be so slight as to become manifest only in auricular flutter. It has been demonstrated experimentally[11] that in the dog under faradically maintained auricular fibrillation the ventricular rate is an index of A-V conductivity and a similar concept should be applicable to the human heart. Thus a ventricular rate over 100 per min. during auricular flutter should be considered normal. Most commonly, A-V conduction delay is caused by digitalis; it may, however, be due to some other cause, as in three of our cases with an initial ventricular rate of less than 80 per min.

The normal A-V conduction time (F-R interval) in auricular flutter with 2:1 conduction was found to be between 0.26 and 0.46 second. This marked and consistent prolongation has an adequate explanation in concealed conduction of the non-conducted alternate auricular impulses.

Abnormal A-V conduction in auricular flutter first appears as a transition of 2:1 to 4:1 ratio and only rarely in the form of 3:1 conduction. In view of this experience, Katz[12] and Ashman and Hull[13] suggested the existence of two levels of block in the A-V junction. The analysis of our cases with a ventricular allorhythmia confirms this assumption. It would appear that the upper region of A-V block represents a normal functional phenomenon associated with the rapid auricular rate, whereas the real block occurs in the lower region of the A-V conduction system. Consequently the latter, if constant, appears as a multiple of the functional A-V ratio of 2:1. Alternating 2:1 and 4:1 conduction can explain more adequately some cases (see fig. 3A) in which a 3:1 ratio has to be considered. A progressive Wenckebach type of A-V block during auricular flutter has been postulated by others[2, 5, 14, 15] for this mechanism. The peculiar grouping of the ventricular complexes in some of our cases with irregular ventricular beating, as demonstrated in figure 2, also displays the typical structure of Wenckebach periods.

The occurrence of uneven conduction ratios during auricular flutter seems unquestionable and is shown in figures 3B and D. This fact does not necessarily exclude the presence of the assumed double region of block, if the effect of the length of the preceding cycle on the conduction of the subsequent impulse is taken into consideration. In their studies on A-V conduction in the mammalian heart, Lewis and Master[16] have clearly demonstrated that the response to a stimulus may depend on the duration of the preceding cycle. Prolongation of this cycle is followed by a longer period of actual and apparent unresponsiveness, and the point at which recovery begins is shifted farther into diastole. However, the conducted or partially conducted beat, terminating this cycle, exerts an influence upon conduction not only of the first impulse that follows, but also of the second one. The diagram in figure 6 demonstrates how the conduction of impulse D is influenced by the degree of penetration of the non-conducted impulse B. The conduction of impulse D is determined (1) by the rest period (r) in the A-V junction between D and the preceding conducted impulse C and (2) by the length of the cycle preceding C (unshaded area). This cycle equals approximately the distance B-C in the upper portion of the A-V junction and the distance A-C in its lower portion. With deeper penetration of B as in figure 6B, the shorter cycle length (B-C) in the greater part of the A-V junction tends to enhance the conduction of impulse D by shortening the refractory period after impulse C. However, the opposite effect of impulse B on the conduction of impulse C shortens the

time of recovery between impulses C and D and thus inhibits the conduction of D. If the latter effect outbalances the former, impulse D fails to be conducted as an indirect result of deeper penetration of the non-conducted impulse B. And furthermore, of two impulses which are both apparently blocked due to a short rest period in the A-V junction, the one occurring after a shorter cycle penetrates deeper into the conduction system. Thus, different conditions of recovery are produced at different levels of the junctional tissues, the total effect of which becomes manifest as success, failure or prolonged duration of a subsequent conduction. It would appear that this

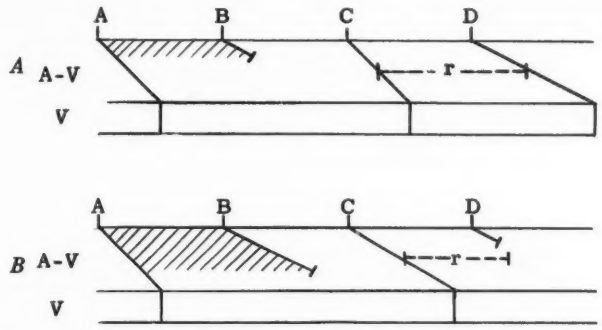

FIG. 6. Schematic diagram to illustrate the influence of the extent of penetration of a non-conducted auricular impulse upon transmission of the next two successive impulses. Discussed in text. Conventions as in figure 1; in addition, A, B, C and D are successive auricular impulses. The broken line (r) indicates the duration of the rest period in the A-V junction. The shaded areas indicate the extent of shortening of a cycle by concealed A-V conduction.

complex mechanism is effective in cases of auricular flutter where no definite A-V ratio can be established (as in 11.8 per cent of our observations listed in table 2).

Actually, our assumption of a constant degree of penetration of the non-conducted impulses into the higher level of the A-V junction where the halving of the rate occurs is a simplification. We know that at this level too, varying penetration occurs which has been assumed to explain the alternation of short and long R-R intervals both in auricular flutter with 2:1 A-V conduction[4] and in sinus rhythm with 2:1 A-V block.[8]

Variations in cycle length are not the only factor controlling the degree of penetration of non-conducted auricular impulses into the conduction system. Lewis and Master[16] have pointed out that deviations from the expected recovery curve occur when conduction is in a critical state as with the last conducted impulse preceding a dropped beat. Undoubtedly, variations in penetration of non-conducted impulses occur under similar circumstances and are responsible for variations in conduction of subsequent beats. This is clearly illustrated in figure 7, which represents a case with Wenckebach periods and concealed A-V conduction during sinus rhythm.* Without appreciable change in the length of the preceding cycle, a non-conducted impulse (5th P wave) in figure 7A penetrates the A-V junction partially, as evidenced by the P-R prolongation of the subsequent beat, or penetrates more deeply (7B) and prevents conduction of the following beat, or (7C) becomes a conducted impulse. Finally, another factor which may also come into play in cases of auricular flutter with depressed A-V conduction is the supernormal phase of recovery which may likewise account for some unexplained variations of A-V conduction.

With a higher degree of conduction delay, an A-V ratio of 6:1 may be produced as in our figure 3C. A 5:1 ratio was not found among our cases, but may occur under conditions

* This case was previously published by H. K. Hellerstein as an instance of atrial infarction, proved at autopsy (Am. Heart J. **36:** 422, 1948).

discussed above. The next step would be 8:1 A-V conduction; however, the low ventricular rate produced with this ratio permits the appearance of nodal escapes which obscure the true A-V ratio. If finally the nodal beats become dominating, the pattern of complete A-V block characterized by regular ventricular rate and varying F-R intervals may appear in the tracing. In one instance of our series (figure 4) incompleteness of the A-V block was manifested by occasional ventricular capture similar to that seen in sinus rhythm.

In figure 5 it was shown that premature beats with aberrant intraventricular conduction appearing during auricular flutter are not always of ectopic origin, but may be produced with A-V conduction if the refractory period of the ventricular muscle is prolonged due to a preceding long ventricular cycle.[17, 18] Thus a ventricular bigeminy can be imitated with variations of the ratio of A-V conduction. If this occurs under digitalis medication, it may be of clinical importance to distinguish between extrasystolic ventricular bigeminy and aberration of intraventricular conduction of transmitted auricular impulses.

Summary and Conclusions

1. Fifty-nine electrocardiograms of auricular flutter obtained on 27 patients were analyzed in order to determine the ratio of A-V conduction and study the factors controlling A-V conduction in auricular flutter.

2. In the untreated patient, an A-V ratio of 2:1 with a constant F-R interval and a regular ventricular rate was most common and a ventricular rate of over 100 was considered evidence of normal A-V conductivity. The 2:1 A-V ratio was explained as a phenomenon of physiological interference of the rapid auricular impulses and the relatively long refractory period of the A-V junction. A persistent 4:1 A-V

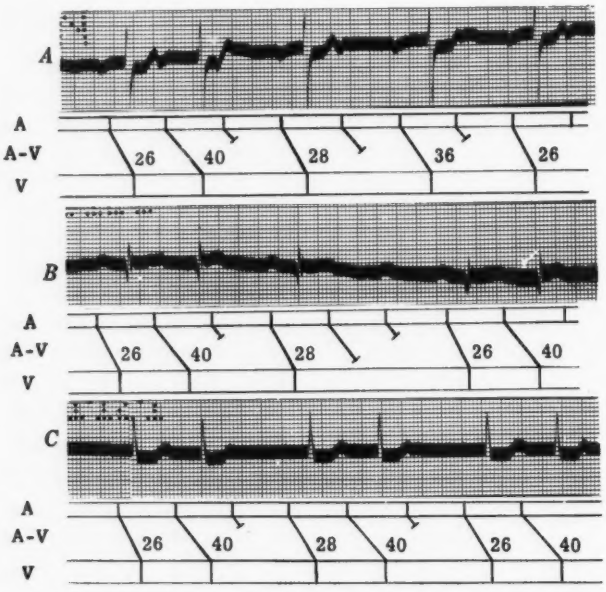

Fig. 7. The effect of the extent of penetration of a non-conducted auricular impulse (fifth P wave) upon the conduction of a subsequent impulse (6th P wave) in a case of sinus rhythm with 2nd degree A-V block. Note that the varying penetration of the fifth auricular impulse does not depend upon the length of the preceding cycle. Conventions as in figure 1. (*A*) Lead CF_2 (*B*) Lead II (*C*) Lead I.

ratio with constant F-R interval or a transition from 2:1 to 4:1 ratio with varying F-R interval was seen most often after digitalization.

3. One-half of the records of auricular flutter with an irregular ventricular rate revealed an arrangement of the ventricular complexes in definite groups identical in structure with the Wenckebach periods observed in cases of sinus rhythm with second degree A-V block. Such records were interpreted as indicating a double region of block, with interference and halving of the auricular rate at the higher level of the A-V junction and block with the Wenckebach phenomenon at the lower, affecting only those impulses which passed the upper region of block.

4. The evidence for the double region of block in cases of auricular flutter with irregular ventricular conduction supports a like explanation for the predominance of even ratios of A-V conduction in auricular flutter.

5. The consistent finding of long A-V conduction times (F-R intervals) in auricular flutter (0.26–0.46 sec.) is ascribed to concealed conduction of non-conducted auricular impulses preceding the conducted ones.

6. Analysis of the records suggests varying extent of penetration of non-conducted auricular impulses as a result of variations of the refractory period of the junctional tissues; such varying concealed conduction is responsible for variations in conduction of the subsequent beats.

7. Penetration into the A-V junction of a non-conducted auricular impulse impairs the conduction of the next impulse and, by so doing, indirectly inhibits also the conduction of the second subsequent impulse; the latter effect is opposite to its simultaneous enhancing effect on the refractory period of this beat, brought about by shortening of the preceding cycle due to the concealed conduction.

8. The complex interplay of the various factors controlling A-V conduction and the unpredictable deviations occurring when conduction is in a critical condition due to the rapid stimulation, are responsible for the failure to unravel the mechanism of A-V conduction in a number of cases of auricular flutter with irregular ventricular response.

9. Premature beats of bizarre contour, appearing during auricular flutter, may be due to activation of an ectopic focus or to aberrant intraventricular conduction of transmitted flutter impulses. The latter interpretation should be considered, if the aberrant beat terminates a short cycle which follows a long ventricular pause.

ACKNOWLEDGMENT

The authors wish to express their gratitude to Dr. Louis N. Katz for his help and criticism.

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ABSTRACTS

BACTERIAL ENDOCARDITIS

Djordjevic, B. S., and Rotovic, A.: The Value of Weltmann's Reaction in the Differential Diagnosis of Subacute Bacterial Endocarditis and Rheumatic Endocarditis. Arch. d. mal. du coeur **42**: 909 (Sept.), 1949.

One hundred ninety Weltmann coagulation tests were performed on 80 cases of subacute bacterial endocarditis and on an equal number of cases of rheumatic endocarditis. The results of this test were compared with the sedimentation rate. The coagulation band was found to be broadened (up to sample 8 or 10) in most of the cases with subacute bacterial endocarditis. It was shortened, normal or only slightly broadened (never over sample 7) in cases with rheumatic endocarditis, regardless of whether heart failure was present or absent. No correlation could be established with the degree of increase of the sedimentation rate. Weltmann's reaction represents a valuable diagnostic method for the distinction of the two types of endocarditis.

PICK

BLOOD COAGULATION

Mosonyi, L., Palos, L. A., and Komaromy, J.: Penicillin and Blood-Coagulation. Acta med. Scandinav. **135**: 458 (Oct.), 1949.

The authors conducted a series of experiments demonstrating that the effect of penicillin on the coagulation of blood depends on the phase in the process of clotting in which the drug is added to the system. If introduced into the circulation, penicillin accelerates coagulation and gives rise to thrombus formation by inhibiting the inactivation of thrombin probably by way of the oxidizing activity of its SH group. However, if penicillin in high concentration is added to the second phase of the clotting system containing fibrinogen either in vitro or by application to the surface of a wound, it acts on the fibrinogen in a manner which inhibits its precipitation. These findings explain the seemingly contradictory observations made by various authors.

SCHWARTZ

Fullerton, H. W., and Anastasopoulos, G.: Anticoagulant Therapy. Brit. M. J. No. 4643: 1492 (Dec. 31), 1949.

According to the authors, in order to prevent intravascular clotting, the clotting time should be maintained at about 30 minutes with heparin. The more efficacious method of accomplishing this is through continuous intravenous drip instead of the usual practice of intravenous injections of 50–75 mg. every four hours.

In the prothrombin test for the control of dicumarol treatment, the authors have substituted viper venom for rabbit brain powder as a source of thrombokinase. However, they point out that when this is done, the greatest possible precautions must be taken to avoid hemolysis. No evidence is presented to show that this modification makes the test any more sensitive than the original method of Quick.

ABRAMSON

Overman, R. S., and Wright, I. S.: The Effect of Aminophylline on the Prothrombin Time of Normal Human Plasma. Am. Heart J. **39**: 65 (Jan.), 1950.

Using the Link-Shapiro modification of the Quick one-stage method for the determination of the prothrombin level, the authors studied the effect of oral administration of clinical doses of aminophylline in 15 normal subjects. This drug had no effect on the prothrombin time determination.

ABRAMSON

Overman, R. S., Newman, A. A., and Wright, I. S.: Plasma Prothrombin Times in Normal Human Subjects. The Effect of Certain Factors on the Prothrombin Time. Am. Heart J. **39**: 56 (Jan.), 1950.

The authors studied the effect of a number of different factors on the prothrombin times of normal subjects. The normal mean prothrombin clotting times, on the basis of 828 determinations on 25 subjects, was found to be 15.8 seconds, with a standard deviation of 1.22 seconds. The ingestion of a meal, strenuous but not prolonged exercise, and a high cholesterol diet did not materially affect the prothrombin time.

ABRAMSON

Horan, F. E., Hirsch, F. G., Wood, L. A., and Wright, I. S.: Surface Effects on Blood-Clotting Components as Determined by Zeta-Potentials. J. Clin. Investigation **29**: 202 (Feb.), 1950.

Zeta-potentials or surface potentials were measured by the authors in silica and silicone-coated

capillary tubes for dilute solutions of blood, serum, plasma, plasma fractions and three anticoagulants (heparin, paritol and "phosphatide inhibitor"). They found that the zeta-potentials of the protein solutions were practically identical at a pH of 6.9. A serum gave a more negative potential than its parent plasma without an anticoagulant and this in turn was more negative than oxalated plasma. The work suggests that either zeta-globules or fibrinogen or both are the essential surface coating protein in plasma. As a general rule, heparin caused the zeta-potentials of the various solutions tested to become more negative but had no effect on bovine crystalline albumin.

BUTTERWORTH

CONGENITAL ANOMALIES

Lequime, J., Denolin, H., and Pannier, R.: Catheterization of the Coronary Sinus in Man. Arch. d. mal. du coeur **42:** 811 (Aug.), 1949.

In a 20 year old patient with cyanosis since childhood the diagnosis of tricuspid stenosis and nonfunctioning right ventricle was based on the following findings: left axis shift in the electrocardiogram and an enlarged left and a small right ventricle in the x-ray examination. During one of several unsuccessful attempts to pass a cardiac catheter into the right ventricular cavity, the tip of the catheter took an unusual course in an upward and backward direction. Blood samples from this position revealed an oxygen content of only 6.39 volumes per cent compared with 13.85 in the blood obtained from the right auricle and 19.44 in blood from the femoral artery. Diminution of pulmonary circulation and its failure to increase on demand was demonstrated by a decrease of the oxygen utilization coefficient during exercise. The authors emphasize the importance of catheterization of the coronary sinus in the study of coronary circulation and of the metabolism of the heart.

PICK

Kjaergaard, H.: Coronary-Arterial Hypoplasia with Paroxysmal Tachycardia and Sudden Death. Acta med. Scandinav. **135:** 439 (Oct.), 1949.

The author describes the clinical course and autopsy findings of a patient who showed congenital hypoplasia of the circumflex branch of the left coronary artery and of the left ventricular wall. The patient, several members of whose family had suffered sudden cardiac deaths, was an apparently healthy woman. At the age of 29 the patient began to have fainting spells which recurred at intervals of approximately one year until the age of 36 when a series of severe attacks occurred. At that time examination revealed the condition to be due to Adams-Stokes attacks resulting from paroxysmal ventricular tachycardia. Two years later the patient died suddenly, presumably during a similar attack and autopsy revealed the underlying cardiac anomaly.

SCHWARTZ

Selzer, A.: Defect of the Ventricular Septum. Arch. Int. Med. **84:** 798 (Nov.), 1949.

The author reports 12 cases of uncomplicated ventricular septal defect in which autopsy was performed, and presents the clinical and pathologic findings in these and in 80 other cases in the literature. Taussig's division of defects of the ventricular septum into "simple" and "high" categories as clinical entities is not confirmed. It is suggested that the typical interventricular foramen is related to the same process of maldevelopment which in severer forms causes the Eisenmenger complex, the tetralogy of Fallot and transposition of the arterial trunks. For that reason, all degrees of transitional forms can be found. The presence of cyanosis may be a more reliable factor in differentiating ventricular septal defect from the Eisenmenger complex than the appearance of the pathologic specimen, since reconstruction of the aortic orifice in its proper relation to the defect during life may be difficult. Smaller defects of the ventricular septum may have no effect on circulatory dynamics, whereas larger ones almost always lead to considerable overloading of the pulmonary circulation with dilatation of the pulmonary artery and hypertrophy, strain, and failure of the right ventricle.

The rough and loud systolic murmur at the lower left sternal border was observed fairly consistently in this series and can be considered pathognomonic for defect of the ventricular septum. There was no apparent relation between the intensity of the murmur and the size of the defect, and loud systolic murmurs were heard in cases of complete absence of the ventricular septum. Early diastolic blowing murmurs at the left sternal border were common.

BERNSTEIN

Tourniaire, A., Devrieux, F., and Tartulier, M.: Ebstein's Disease. Arch. d. mal. du coeur **42:** 1211 (Dec.), 1949.

The authors present a case of Ebstein's syndrome (congenital downward displacement of the tricuspid valve into the right ventricle and patent foramen ovale) in a 39-year-old woman who had no history of rheumatic fever or other diseases. She had frequent attacks of supraventricular tachycardia but manifested no other cardiac symptoms. The electrocardiogram revealed a right bundle branch block. X-ray examination showed a markedly enlarged right heart and calcification of the tricuspid valve. Tricuspid insufficiency was recognized clinically and confirmed by catheterization. Tricuspid insufficiency can be diagnosed by physical examination and from the hepatic and jugular tracings. The combination of this valvular defect with the patency of the fora-

men ovale can be diagnosed definitely only by means of angiocardiography or catheterization.

LUISADA

Abbott, O. A.: Congenital Aneurysm of Superior Vena Cava. Ann. Surg. **131:** 259 (Feb.), 1950.

The author reports a case of primary aneurysm of the superior vena cava in a 19 year old white male. Since angiocardiographic studies revealed a fusiform dilatation of the vessel, exploratory thoracotomy was performed. Multiple grape-sized small aneurysms were found on the antero-medial surface of a large aneurysmal sac attached to the superior vena cava. The entire vessel was surrounded by cellophane. Several months later angiocardiographic examination revealed a definite reduction in size of the aneurysm.

ABRAMSON

CONGESTIVE HEART FAILURE

Zak, E. R.: Liver Function in Cardiac Failure. Acta med. Scandinav. **134:** 423 (Nov.), 1949.

The author reviews the role of the liver in cardiac failure, particularly in regard to altered hemodynamics and water metabolism. Engorgement of the liver in cardiac failure may be either passive or active. Passive congestion accompanied by elevated venous pressure is best seen in severe cardiac failure. However, an enlarged liver may precede the rise in venous pressure. Among 30 cases of cardiac failure with enlarged liver collected at random by the author, a normal venous pressure was observed in 9 cases. Findings of this type can be explained by a throttle mechanism of the liver veins mediated by smooth muscle sphincters. These are probably stimulated to contract by reflex action originating in the right heart with resultant active congestion of the liver.

In both liver disease and in cardiac failure with chronic liver congestion an intracutaneous wheal of sodium chloride solution disappears more rapidly than in the normal subject. This finding indicates an increased avidity for water on the part of the skin in these abnormal conditions. The inability of the diseased liver to destroy the antidiuretic hormone may play a part in this process, although sodium retention by the kidney may be the decisive factor. The author has demonstrated that this altered behavior of the skin affects the spreading of other intracutaneously injected matter, such as blood, trypan red, or histamine-like substances.

This reduced permeability of the skin is accompanied by reduced water evaporation and sweat secretion from the skin observed in chronic congestive failure. Damage to the liver due to long standing congestion may be responsible for reduced insensible perspiration. In studies of liver damage caused by chloroform or carbon tetrachloride it has been shown that there is a resultant decrease in insensible loss of water from the skin.

SCHWARTZ

Scébat, L., Maurice, P., and Lenègre, J.: Action of a Mercurial Diuretic on the Right Heart of Cardiac Patients. Arch. d. mal. du coeur **42:** 1149 (Dec.), 1949.

Right heart catheterization was performed in 8 cardiac cases during and after intravenous injection of a mercurial diuretic (Novurit). Both right auricular and right ventricular pressure were markedly decreased after the injection. The effect started within 13 minutes and lasted from 30 to 80 minutes. The pressures of the right cardiac chambers were lowered from 25 to 30 per cent. The use of mercurial diuretics in the emergency treatment of paroxysmal pulmonary edema is suggested. Three cases treated by the authors manifested a very favorable course.

LUISADA

Scheinberg, P.: Cerebral Circulation in Heart Failure. Am. J. Med. **8:** 148 (Feb.), 1950.

In 16 observations on 14 patients in congestive heart failure with low cardiac output the mean cerebral blood flow was 39 per cent less than the mean for normal young subjects. Since the average reduction in cardiac output in a comparable group was 41 per cent, the reduction in blood flow to the brain may be considered proportionate to the fall in cardiac output. Although the mean increase in cerebral arteriovenous oxygen difference of patients with congestive failure was 41 per cent over that for normal subjects this did not compensate for the decrease in mean cerebral blood flow, for the mean cerebral oxygen consumption was reduced significantly below the normal value. Cerebral glucose utilization was also reduced. Cerebral vascular resistance was increased 100 per cent over the normal. It is considered that rise in venous pressure and thus in intracranial pressure are little if at all related to this increased resistance. These studies are compatible rather with the assumption that the increase in resistance in the cerebral vessels results from vasoconstriction.

LEVINE

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Morrison, L. M., and Johnson, K. D.: Cholesterol Content of the Coronary Arteries and Blood in Acute Coronary Artery Thrombosis. Am. Heart J. **39:** 31 (Jan.), 1950.

The cholesterol content of the anterior descending branch of the left coronary artery, the blood serum cholesterol and ester levels, and the gross appearance of the aorta and coronary arteries (for evidence of atherosclerosis) were studied in 11 patients who had died of acute coronary artery thrombosis

and in a comparable group of 14 patients who had died of causes other than coronary artery thrombosis. The average age for the 2 groups was 64 and 62 years, respectively. The average cholesterol content of the coronary artery was 20.4 mg. per Gm. of dried coronary artery weight, with a range of 8.1 to 36.5 mg. in the acute thrombosis group. This value was found to be 5.1 mg. with a range of 0.6 to 8.1 mg. in the control group. The average blood cholesterol was 303 mg. with a range of 210 to 411 mg. in the acute thrombosis group, whereas it was 186 mg. with a range of 148 to 241 mg. in the control group.

It is concluded that these findings suggest a disturbance in lipid metabolism as a factor in the pathogenesis of atherosclerosis.

SCHWARTZ

Fagin, I. D., and Chapnick, H. A.: Clinical Patterns of Myocardial Infarction in Ambulant Patients. Ann. Int. Med. **32**: 243 (Feb.), 1950.

The electrocardiograms of a gainfully employed group of workers subscribing to a union health service were reviewed. From this group, the case histories of 100 persons whose electrocardiograms displayed evidence of recent or antecedent myocardial infarction and who were ambulatory, were selected for more detailed analysis in order to correlate the clinical findings with the electrocardiographic abnormalities. It was noted that only 52 of this number had presented a symptom complex typical of acute coronary occlusion though many of these had been so diagnosed in retrospect after the results of electrocardiographic studies were obtained. In 7 patients, myocardial infarction was an incidental electrocardiographic finding; these patients presented no cardiac symptoms. Forty-one patients had only mild symptoms suggesting cardiac insufficiency such as exertional angina and/or dyspnea. Of the whole group, only 6 were totally disabled; the others were able to continue at their jobs even though some had intermittent symptoms suggestive of coronary or myocardial insufficiency.

WENDKOS

Zinn, W. J., and Cosby, R. S.: Myocardial Infarction. I. Statistical Analysis of 679 Autopsy-Proven Cases. Am. J. Med. **8**: 169 (Feb.), 1950.

In a statistical study of 679 necropsies on patients, showing old or recent myocardial infarction the authors found that the age at death averaged 67.8 years. This study, contrasting with most previous reports, showed no significant difference between the sexes in incidence or in age at death when considered in relation to the incidence and age at death in both sexes in the general autopsy population (5943 deaths) during the same period. The mortality rate with single infarcts and the incidence of rupture was greater among women than among men and infarction tended to occur a few years earlier in women than men. It seemed that women are more likely than men to suffer a fatal outcome from an initial infarct, which is evidence perhaps of an inadequate collateral circulation in women. There was no striking evidence that hypertension is more common in female than in male victims of myocardial infarction. There was a distinctly lowered incidence of myocardial infarction among Negroes but it was felt that the significance of this change cannot be evaluated at this time. There was a greater incidence of infarction among diabetic women than among women in the entire sample. The average age at death among the diabetic group was 3.6 years younger than that for the general series. The immediate prognosis of the acute attack is much more serious in the diabetic than in the nondiabetic. The evidence suggested to the authors that the difficulty in the control of the diabetic state itself, and not the structural arterial alterations, is the primary factor in shortening the life expectancy of these diabetics.

LEVINE

Bogoch, A., and Christopherson, E. F.: Calcified Cardiac Aneurysms. Ann. Int. Med. **32**: 295 (Feb.), 1950.

On the basis of personal experience with 2 cases, and on the basis of a review of the findings in previously reported cases in the medical literature, the authors discuss the radiologic detection of calcification in the cardiac region as an aid in the diagnosis of a ventricular aneurysm secondary to myocardial infarction. Calcification in the wall of such aneurysms is a relatively uncommon occurrence. The calcification may involve the laminated clot or the wall of the aneurysmal sac. Calcification of a cardiac aneurysm has to be differentiated from calcified pericardium such as may occur in constrictive pericarditis. In aneurysm, the calcified shadow is usually linear, limited to the left ventricle, and situated within the heart contour. Pericardial calcification produces a thicker and more irregular shadow not restricted to the left ventricle and situated outside the heart contour. Electrocardiographic study helps to differentiate these two causes of calcification in the cardiac region inasmuch as the changes indicative of antecedent myocardial infarction would tend to support the diagnosis of a calcified ventricular aneurysm. Calcification of a ventricular aneurysm may become evident radiologically within a short period of time or it may take years to develop.

WENDKOS

ELECTROCARDIOGRAPHY

Zemplenyi, T.: Synchronic Registration of Standard and Unipolar Limb Leads by the "Differential Method." Casop. lek. cesk. **88**: 1376, 1949.

The Swedish three beam electrocardiograph (System Elmquist) is constructed in such a way that one

oscillograph (Lead III) inscribes the difference between the curves registered by the two others (Lead II minus Lead I). By an appropriate connection of the patient with the system the author was able to register simultaneously two of the "unipolar" limb leads and the standard lead derived automatically from them. If a correct technic is used; such differential leads are identical with the respective standard (bipolar) leads, obtained in the customary way. The main advantage of the method, which was tried out in 320 routine examinations, consists in the synchronous registration of standard and "unipolar" limb leads, which enables one to study their relationship in a very clear and instructive manner.

PICK

Soulie, P., Laham, J., and Papanicoliés, I.: Electrocardiographic Study of Parietal Aneurysms of the Apex of the Heart. Arch. d. mal. du coeur **42:** 869 (Sept.), 1949.

Following a study of 15 cases (7 with necropsy) of apical aneurysm and a review of the literature, the authors arrived at the following conclusions: A ventricular aneurysm should be considered if, in the presence of signs of apical infarction, a marked axis deviation either to the right (+ 120° to −90°) or to the left (−70° to −90°), is found in the electrocardiogram. Similarly, posterolateral infarcts with low voltage in left-sided precordial leads and left axis deviation (−70° to −90°) are suggestive of a ventricular aneurysm. Axis deviation progresses with the development of an aneurysm. It seems that aneurysms following infarction of a heart which was previously not enlarged have a tendency to produce right axis shift, in contrast to the production of left axis shift if an aneurysm develops in a heart with marked hypertrophy. Persistence of RS-T deviations can accompany these changes. The electrocardiogram has a definite value in the diagnosis of a ventricular aneurysm; however, absence of the described changes does not exclude the presence of an aneurysm.

PICK

Fumagalli, B.: Unipolar Interpretation of the Peripheral Electrocardiogram. Arch. d. mal. du coeur **42:** 891 (Sept.), 1949.

The author claims that there is no fundamental difference between "unipolar" and "bipolar" limb leads. By means of experiments the author tried to prove this assumption, which is derived from theoretic considerations. To a conventional, normal or abnormal electrocardiogram he added a reversed Lead V_R. He found that if the different leads are arranged in the order, V_L, 1, $-V_R$, 2, V_F, 3, a gradual transition of upright to inverted QRS-T complexes can be seen. In the author's opinion this proves that each of these leads, whether "unipolar" or "bipolar," represents the projection of the frontal vector upon a different frontal axes two of which always form an angle of 30°. The series of leads used by the authors can therefore be properly designated by the symbols $V_{-30°}$, V_0, $V_{30°}$, $V_{60°}$, $V_{90°}$, $V_{120°}$.

According to the author's concept, the standard limb leads do not represent complex leads derived from the unipolar leads, but both sets of leads have the same origin. Unipolar limb leads can therefore not replace the standard leads, but only add to the information gained by the latter. A modern electrocardiogram consists of two phases of exploration, one in the frontal plane (limb leads) and another in the horizontal plane (precordial leads).

PICK

Coraboeuf, E., and Weidmann, S.: The Potential of the Cardiac Muscle at Rest and during Activity Measured by Penetrating Electrodes. Compt. rend. Soc. de biol. **143:** 1329 (Oct.), 1949.

The authors measured the potential within isolated Purkinje fibers of the dog's heart by inserting microelectrodes through the cellular membrane. The magnitude of the rest potential was found to be 60 to 82 mv, (the average of 11 measurements was 71 mv). These values exceed the values found for surface potentials. The true intracellular values may be larger since shunts produced by the manipulation of the membrane cannot be excluded. During activity of the fiber the potential returned to zero level without "overshooting." After several hours of observation it was noted that the change from rest to activity potential occured less abruptly and to a lesser extent.

PICK

Coraboeuf, E., and Weidmann, S.: Action Potentials of the Heart Muscle Obtained by Intracellular Microelectrodes. Presentation of a Reversion of Potential. Compt. rend. Soc. de biol. **143:** 1360 (Oct.), 1949.

Experimenting under more physiologic conditions on the isolated Purkinje fiber of the dog's heart, the authors obtained values for the intracellular rest potential of 75 to 80 mv. With the improved technic they were able to demonstrate an "overshooting" of the action potential beyond the zero level, which they had failed to observe in previous experiments.

PICK

Unghvary, L.: The Cause of the Electrocardiographic Changes from Arborization Block. Cuore e circolaz. **33:** 257 (Oct.), 1949.

Experimental studies on dogs are reported in which either a branch of the bundle of His was cut, or the coronary sinus ligated. Ligation of the coronary sinus caused venous stasis in the myocardium followed by low voltage. The combination of low voltage due to venous stasis plus the typical bundle branch block pattern was similar to the electrocardiographic pattern which has been called "arborization block".

The author, therefore, attributes the "arborization block" pattern to the combination of bundle branch block and venous stasis which is quite common as a result of heart failure.

LUISADA

Biocca, P., Masini, V., and Sposito, M.: Electrocardiographic Studies after Pneumonectomy and Lobectomy. Cuore e circolaz. **33:** 292 (Oct.), 1949.

Electrocardiographic changes were found in 58 per cent of the patients on whom pneumonectomy or lobectomy had been performed. In 16 per cent of cases, there was high voltage of the P wave. This was interpreted as evidence of slight auricular damage following surgery. Alterations of the S-T segment were found in 52 per cent of the cases. In the first days after the operation, these S-T segments had the form typical of acute pericarditis (elevation of S-T in all leads) and were transitory. In some cases, late permanent alterations of the T wave were observed (flat or inverted T wave of low voltage), especially in Leads I, II, V_4 and V_6. This was interpreted as evidence of myocardial damage following initial pericarditis. After surgery, premature beats were observed in 14 per cent of cases and auricular fibrillation in 5 per cent. The latter was considered to be related to auricular damage. The electrocardiographic patterns were not closely related to the clinical conditions, the postoperative course, or suppurative complications.

LUISADA

Scherf, D., and Terranova, R.: Mechanism of Auricular Flutter and Fibrillation. Am. J. Physiol. **159:** 137 (Oct.), 1949.

The topical application or subepicardial injection of aconitine (0.05 cc. of a 0.05 per cent solution of aconitine crystals, Merck) into the head of the sinus node induced auricular fibrillation after vagectomy in 27 adult dogs. Cooling the site of injection changed the fibrillation activity to flutter and then resulted in auricular paralysis. Fibrillation reoccurred on warming. In some instances the flutter resulting from cooling was of low rate with long auricular pauses between the cycle, with records resembling auricular paroxysmal tachycardia with A-V block. Alternation of cycle length during flutter was frequently present. Normal sinus rhythm was reestablished by local application of potassium or quinidine.

The authors advance their hypothesis that auricular flutter and auricular fibrillation are the result of rapid stimulus formation in one center with the appearance of islets of refractory tissue in the auricles (previously postulated by Lewis) forcing the excitation wave to take a circuitous path. Although vagal stimulation inhibits auricular activity in sinus tachycardia and certain types of auricular paroxysmal tachycardia, it increases the rate of auricular activity in the aconitine-induced irregularities. It is speculated that stimuli which are inhibited by vagal stimulation are rhythmically formed while auricular fibrillation and flutter and the aconitine irregularities are the result of continuous stimulation. The auricular response in the latter would then depend on the refractory period of auricular tissue and the changes induced by vagal stimulation would be the result of a shortening of the refractory phase induced by vagal stimulation.

HECHT

Unghvary, L.: Changes in the Position of Frontal and Spatial Axes during the Development of the Heart and Their Relation to Precordial Leads. Ztschr. f. Kreislaufforsch. **38:** 674 (Nov.), 1949.

In 300 healthy individuals ranging in age from infancy to 60 years, the author determined the direction of the electrical axis of QRS and T. The direction in the frontal plane was constructed from the standard leads; to determine the axis in a horizontal plane the author used two leads, the first in anteroposterior direction in the midline, the other from the right to the left midaxillary line. From infancy to the age of 60 years the R axis changes in the frontal plane from about + 100° to 0° and in the horizontal plane from +40° to −40°, i.e. from an anterior direction to a backward direction. At the same time a shift of the T axis can be noted. In the frontal plane it first shifts from 0° to +60° and then again back to 0°. The change in the horizontal plane is the same as that of the R axis. The author concludes from this study that an inverted T wave in CF_4 can be considered abnormal only in persons over 15 years; in CF_2, only in persons 30 years of age. The change of the axes with increasing age occurs more slowly in females than in males.

PICK

Gadermann, E., and Renner, W.: An Investigation of the Relationship of Hypertension and Pulmonary Emphysema with Special Reference to Electrocardiographic Findings. Ztschr. f. Kreislaufforsch **38:** 652 (Nov.), 1949.

Of 450 patients with essential hypertension one-third were found to have clinical and roentgenologic manifestations of pulmonary emphysema. The average blood pressure values (190/100) were found to be identical in patients with and without emphysema. Heart failure was found to be present in half of the patients with emphysema and in only one-fourth of the patients without emphysema. A comparative study of the electrocardiograms of both groups revealed no significant differences as far as axis deviation was concerned. Marked sinus arrhythmia and P pulmonale were found more often in the group with emphysema. A correlation of abnormal electrocardiographic findings with the presence of heart failure was possible only in cases of hypertension without pulmonary emphysema or in those cases of the combined disease who had a marked left axis devia-

t on in the electrocardiogram. The author concludes t at the electrocardiogram is only of minor diagnos- t c and prognostic value in patients with hyperten- s on and concomitant pulmonary emphysema.

PICK

Kuehns, K.: The Value of the Ergotamine Test in the Interpretation of Abnormal T Waves. Ztschr. f. Kreislaufforsch. **38:** 669 (Nov.), 1949.

The author observed experimentally in rabbits that T-wave changes produced by adrenaline and considered to be coronary in origin could be prevented by injection of Hydrergin (hydrated ergot alkaloid). In two clinical cases, changes indicative of coronary disease disappeared after treatment with the same drug. The author concludes that ergot alkaloids exert a direct effect on the coronary blood flow and the metabolism of the heart muscle. The value of the ergotamine test for the distinction of T-wave anomalies due to organic myocardial disease from those due to a vegetative dystonia is doubtful.

PICK

Oppenheimer, M. J., Long, J., Durant, T. M., and Wester, M. R.: Relation of Intraventricular Dielectrics to Unipolar Leads. Am. J. Physiol. **159:** 476 (Dec.), 1949.

By filling the right ventricle with the dielectric CO_2, the authors attempted to study the genesis of the electrocardiogram. With the dog in the supine position, there are (1) reduced QS and an increased R in V_R; (2) a similar but smaller increased R in V_L; (3) increased QS and decreased R in V_F. These and other results which were found when the heart was shifted, lend support to a "zonal interference" concept of the genesis of the electrocardiogram.

MOKOTOFF

HYPERTENSION

Smithwick, R. H.: An Evaluation of the Surgical Treatment of Hypertension. Bull. New York Acad. Med. **25:** 698 (Nov.), 1949.

The author states that in his own experience 66 per cent of unselected hypertensives with cardiovascular changes have a slight to marked reduction in blood pressure lasting one to five years but this falls to 47 per cent for the five to ten year follow-up group. The operative mortality is about 1 per cent but is higher if a transthoracic approach to include cardiac innervation is used. This latter technic is used in about 20 per cent of cases because of tachycardia and postural hypotension. Evaluation of all cases after five to ten years indicates that hypertension is favorably modified by sympathectomy as judged by eye grounds, electrocardiograms, blood pressure and total mortality, although the author admits the difficulty of finding comparable case reports on unoperated hypertensives.

BUTTERWORTH

Tibbetts, R. W.: Leukotomy and Hypertension. A Case Report. Brit. M. J. No. 4642: 1452 (Dec.), 1950.

The author presents the case report of a woman, age 54, who suffered suicidal depression, headache, disturbed vision with retinal hemorrhages and a blood pressure as high as 260 systolic over 160 diastolic. Following a prefrontal leukotomy her blood pressure dropped to 160 systolic over 90 diastolic with complete relief of her headaches and retinopathy. The author feels that results such as this occur only when a high degree of nervous tension underlies the hypertensive state prior to surgery. Leukotomy, by relaxing the nervous tension, is thought to be responsible for the result obtained. The question as to whether pressor substances have anything to do with producing such hypertension or whether thalamofrontal radiations are responsible is briefly discussed.

TANDOWSKY

Koppermann, E.: The Hemodynamic Picture of the Circulation in Hypertensive Patients before and after Treatment by Salt Free Diet and Bed Rest. Ztschr. f. Kreislaufforsch. **39:** 2 (Jan.), 1950.

The author reports his hemodynamic observations on 94 hypertensive patients divided into four groups. In the first group cases of essential hypertension, hypertonicity of the vessels of the optic fundus invariably was found. In the second group, hypertensives of older age, sclerotic changes of the fundi were more prominent. A third group, transitional between groups 1 and 2, showed an incipient retinitis angiospastica with more marked and stable elevation of systolic and diastolic pressures. A last group, patients with malignant sclerosis, showed some impairment of renal function, advanced retinitis and an abnormally high diastolic pressure. None of the patients was in heart failure. In all four groups of patients the cardiac output and the peripheral resistance were calculated by the method of Wesler and Boeger before and after treatment by salt free diet and bed rest. A decrease of peripheral resistance and normalization of the declining output could be noted in all four groups of hypertensive patients. This observation suggests a common primary vascular mechanism in the pathogenesis of all forms of hypertension.

PICK

Koppermann, E.: The Dynamics of the Circulation in "Pale Hypertension" before and after the Onset of Renal Failure. Ztschr. f. Kreislaufforsch. **39:** 10 (Jan.), 1950.

The author reports his hemodynamic studies of 7 patients with primary vascular hypertension. With the onset of renal failure a marked increase of the peripheral resistance and a drop of the minute volume below normal values was noted. With progression of renal failure pulse pressure and minute

volume increased, while the values calculated for the peripheral resistance became lower. The latter changes could possibly be related to the retention of substances normally excreted by the kidneys and to the development of anemia and hydremia or to both.

PICK

Friedenberg, S.: A Low-Sodium Diet for Hypertensive Vascular Diseases Precipitating Addison's Disease and Miliary Tuberculosis. New England J. Med. **242:** 277 (Feb.) 1950.

The author discusses complications resulting from the use of a low sodium diet in the treatment of hypertensive cardiovascular disease and presents a case in which Addison's disease and miliary tuberculosis were precipitated by use of such a diet. A 63 year old housewife with a history of hypertension of 4 years duration was placed on a low sodium diet to control blood pressure. She steadily became weaker until 5 months later when she was admitted to a hospital presenting the clinical picture of an addisonian crisis. She recovered after treatment with adrenocortical extract and other supportive measures. During the hospital stay a diagnosis of miliary tuberculosis was also made and she received 30 Gm. of streptomycin over a 30 day period. The course of treatment was then interrupted by her unwillingness to remain in the hospital. Because of circumstances at home adrenocortical extract was not administered regularly and she returned to the hospital 4 months later in much the same condition as at the first hospitalization. She again responded to therapy, but a month after admission died suddenly. Postmortem examination proved death to be due to miliary tuberculosis and adrenal insufficiency.

The author presents the possibility that a low sodium diet over many weeks may disrupt adrenocortical function, and this in turn, lowering defense mechanisms, may activate quiescent miliary tubercles.

NADLER

Arnold, H.: The Genesis of Arterial Hypertension. Deutsche med. Wchnschr. **75:** 281 (March), 1950.

The author observed the development of transient and permanent hypertension following infectious diseases like scarlet fever, diphtheria, angina lacunaris, typhoid fever, epidemic hepatitis, icterus infectiosus, and malaria. He presents diagrams of the clinical course of 4 patients, one of whom died following scarlet fever and at autopsy did not show "chronic nephritis" but scars in the kidneys from pyelonephritis.

The author presents a critical analysis of the present concepts of hypertensive disease. In his opinion, the Goldblatt mechanism is insufficient to produce persistent hypertension in patients with no predisposition to arterial disease. The latter condition can be inherited or acquired. Adequate stimuli, such as disturbances in regulation of vascular reactions following infectious diseases, may give rise to permanent arterial disease leading to sustained hypertension. Primary renal hypertension does not exist in human pathology.

PICK

Hawthorne, E. W.: Experimental Renal Hypertension in the Dog following Renal Ischemia. Proc. Soc. Exper. Biol. & Med. **73:** 353 (March) 1950.

The author studied the effect of preliminary renal ischemia produced by bilateral renal artery occlusion for two, four, five and six hours on subsequent experimental renal hypertension production on 19 dogs. The experimental renal hypertension was produced by a standard technic of renal artery constriction. The results suggest that previous renal damage of either a mild or a severe degree has an effect on experimental renal hypertension. Seven dogs receiving mild renal injury showed a very high rise in mean arterial pressure in the first month following bilateral renal artery constriction and a subsequent fall in pressure to near normotensive levels. Four dogs that survived more severe renal damage showed slight to no rise in mean arterial pressure during the first three or more months following bilateral renal constriction. Of the 4 dogs who survived severe renal damage, one showed an abrupt rise in mean arterial pressure in three months and another in five and one-half months after bilateral renal artery constriction.

MINTZ

Wilkins, R. W.: Veratrum Viride and Essential Hypertension. New England J. Med. **242:** 535 (April), 1950.

The author reviews the current studies evaluating the use of veratrum viride in the therapy of essential hypertension. The hypotensive effects have been shown to be vasodilator mediated from the central nervous system. After therapy with this drug, the cardiac output does not decrease but may increase; the renal and portal blood flow decreases intially but returns to normal when the blood pressure stabilizes.

The beneficial effects of this drug are illustrated in a study of 34 patients. The arterial blood pressure was decreased in 80 per cent of this group. Only rarely did the blood pressure return to normal. In general, signs and symptoms were favorably affected or unchanged in patients whose arterial pressures were lowered. Untoward effects were nausea and vomiting and collapse reactions. Though disturbing, they generally did not necessitate discontinuance of the drug.

NADLER

Mennell, E. R., and Gregg, D. E.: A Small Adjustable Renal Artery Clamp for Production of Chronic Hypertension in the Rat. Proc. Soc. Exper. Biol. & Med. **73:** 645 (April), 1950.

A small adjustable silver clamp, modeled after the larger Goldblatt clamp, was designed and applied to both renal arteries of rats in order to induce chronic hypertension. Blood pressures, before and after operation, were determined in the hind leg of 11 unanesthetized rats by a modification of the method of Kersten and co-workers. Control blood pressures before operation varied from 100 to 125 mm. Hg. Eight of the rats attained a blood pressure level of at least 160 mm. Hg within 8 to 21 days after the clamps were applied at one operation to both renal arteries. In 2 rats such an elevated blood pressure developed somewhat later. One rat died with massive infarcts of both kidneys after the application of the clamps. The blood pressures remained elevated (160 up to a maximum of 220 mm. Hg) for months in 9 of 11 rats.

MINTZ

Martorell, F.: Hypertensive Ulcer of the Leg. Angiology **1:** 133 (April), 1950.

According to the author, the hypertensive supramalleolar ulcer is the result of ischemia secondary to obliterative lesions of the small arterioles resulting from hypertension. The lesions are specific and are similar to those found in other localities in hypertensive patients. Clinically the ulcer is bilateral and symmetrical, painful, resistant to treatment, and unrelieved by bed rest. There is no visible circulatory change in the lower extremities and usually no edema. The diagnosis is based on hypertension in the upper and lower extremities, characteristic anterolateral location of the ulcer, the finding of perceptible pulses in all arteries of lower limbs, and no disturbance of the venous circulation. Lumbar sympathectomy will heal the ulcer. Thirteen case reports are included.

WESSLER

PATHOLOGIC PHYSIOLOGY

Hilden, T.: On the Pathogenesis of Acute Pulmonary Edema. Acta med. Scandinav. **136:** 162, (Suppl. 234), 1949.

In paroxysmal nocturnal dyspnea and acute pulmonary edema associated with hypertension many hemodynamic and neurogenic factors are known to be involved. To clarify the position of cardiac output in this scheme the author describes two mechanisms for increasing the output: (1) increased emptying of the left ventricle, and (2) increased filling from the veins. The emptying mechanism is at work when the increased cardiac output is due to a decreased peripheral resistance; it causes a decrease in pulmonary congestion. The filling mechanism applies when there is an increased venous return; it increases pulmonary congestion. This becomes active in recumbency.

In the transition from rest to work heart size is not increased nor is vital capacity decreased (consistent with an emptying mechanism), in the transition from an erect to a recumbent position the heart size is increased and vital capacity reduced (consistent with a filling mechanism). Therapeutically, the filling mechanism is interrupted by the erect position, tourniquet, venesection, aminophylline and morphine. Reducing the blood pressure starts the emptying mechanism, aminophylline, concentrated glucose and tetraethylammonium bromide are useful.

WAIFE

PATHOLOGY

Nieth, H.: Histologic and Cytologic Studies of the Human Heart Muscle Following Hypertrophy and Failure. Beitr. Z. Path. Anat U. Z. allg. Path. 110: 618 (Dec.), 1949.

The author studied the histologic changes of different parts of the right and left ventricle in 25 hearts with hypertrophy and compared them with changes in 8 normal hearts. In hypertrophic muscle fibers the nuclei were found to be enlarged and spherical. Frequently a double nucleus or a chain of nuclei was present. In some of the fibers multiple nuclei were found in an irregular arrangement. The increase of size of the muscle fibers was due to a thickening of the fibrils without significant increase of the content of sarcoplasm. With marked hypertrophy, necrosis and scar tissue were found in certain areas of predilection mainly in the subendocardium of the affected ventricle. These changes, ascribed to chronic coronary insufficiency, are the most important factor in the development of failure of a heart with hypertrophy.

PICK

Kiloh, G. A.: Pure Aortic Stenosis. Brit. Heart J. 12: 33 (Jan.), 1950.

The author analyzes the clinical features of 27 instances of pure aortic stenosis occurring in subjects under the age of 50 years. Of these 27 cases 26 did not give a history of rheumatic fever; 20 were male. Only 8 gave symptoms of cardiac disease. Of the 15 cases seen personally an aortic thrill was palpable in all and in only one instance was the apical impulse abnormal. The second aortic sound was normal in 11 and diminished in intensity in 4 patients. The blood pressure was normal in all. Twelve had normal electrocardiograms. Three showed left ventricular preponderance. X-ray showed moderate cardiac enlargement in 2, slight enlargement in 12 and no enlargement in 1. The ascending aorta was prominent in 14 of 15 cases that had roentgenograms and calcification of the aortic valve was seen in 8 of these

15 patients. On the basis of these findings, the author believes that this lesion cannot be differentiated from subaortic stenosis except possibly by angiocardiography. He doubts that the lesion is of rheumatic origin.

SOLOFF

Fisher, B., and Salmons, J. A.: Healing Incomplete Spontaneous Rupture of the Aorta. Arch. Path. **49**: 27 (Jan.), 1950.

This is the case report of a Negro man, aged 56 years, with hypertension (240/150), who originally complained only of left-sided chest pain and dyspnea but ultimately died of progressive congestive heart failure. Necropsy revealed a transverse rupture of the intima of the aorta, involving almost the entire circumference 2.5 cm. above the sinus of Valsalva. There was a small zone of dissection in each direction from the rupture, but the rupture was incomplete and the entire lesion was covered by an endothelial surface. The adventitial was uninvolved. Microscopically there was an endothelial layer covering the interrupted portions and continuous with the intact margins of the aorta above and below the rupture.

The authors comment upon the infrequency of this lesion, and emphasize that it may be missed at autopsy if the aorta is cut off shortly above the valve ring. It is of interest that such an extensive tear involving almost the entire circumference remained incomplete, and that death occurred from congestive heart failure instead of aortic rupture with hemopericardium.

GOULEY

PHARMACOLOGY

Sanabria, A.: Cytochrome "C" and Anoxia. Arch.d. mal. du coeur **42**: 915 (Sept.), 1949.

The author reports his experience in the treatment of patients with signs of defective tissue oxygenation by daily intravenous injection of oxygenated cytochrome C in doses of 20 to 100 mg. Some improvement could be observed in cases with Adams-Stokes syndrome, in cases of intermittent claudication and in certain cases of pulmonary emphysema. No effect was obtained in 5 cases with angina pectoris, in one case of myocardial infarction and in two cases with advanced heart failure. In a case of arterial hypertension with persistent symptoms after sympathectomy, application of cytochrome C was followed by remarkable subjective improvement and a marked drop of blood pressure. Toxic signs observed during the treatment were urticaria and chills; there were febrile reactions in some cases.

PICK

Raab, W.: Propyl Thiouracil for Angina Pectoris. Acta med. Scandinav. **135**: 364 (Oct.), 1949.

Nine patients with angina pectoris were treated over periods of from 5 to 16 months with daily doses of propyl thiouracil ranging between 100 and 300 mg. One patient responded with complete disappearance of symptoms which remained absent 19 months after discontinuation of the medication. There was a marked reduction in the number and severity of attacks in 4 others, improvement was moderate in one case, slight in another, and in 2 patients there was no response. Improvement occurred on an average approximately 10 weeks after the beginning of therapy. The initial basal metabolic rate did not materially influence the results and there was no close correlation between the degree of diminution of the basal metabolic rate and the degree of improvement.

Toxic side effects were not noted. In one case there was a transient slight leukopenia. There were 3 instances of fatal coronary occlusion during treatment, and 2 others occurred 3 weeks and 6 months, respectively, after propyl thiouracil therapy was discontinued. In addition there was one nonfatal coronary infarction which occurred during treatment. Although this death rate appears high and there may be a connection between the treatment and resulting hypercholesterolemia, it is pointed out that in another series of 10 propyl thiouracil–treated cases no instance of coronary infarction or death was reported.

It is suggested that combining propyl thiouracil therapy with x-ray irradiation of the adrenals may prove to be even more effective in angina pectoris by reducing the specific effects of epinephrine and sympathin upon the myocardium.

SCHWARTZ

Lippman, R. W.: Effect of Proteinuria on Toxicity of Mercurial Diuretics in the Rat. Proc. Soc. Exper. Biol. & Med. **72**: 682 (Dec.), 1949.

The administration of human albumin to rats, with resultant proteinuria, prior to the giving of mercurial diuretics sharply reduces the renal toxicity of the mercurial. This effect is attributed to inhibition of mercurial reabsorption when the tubules are saturated with protein. The simultaneous administration of human albumin and the mercurial diuretic enhances toxicity. This effect is attributed to the more rapid absorption of the mercurial, concomitant with more rapid reabsorption of protein during the tubular loading phase.

MINTZ

Norcross, J. W.: Quinidine as a Cause of Thrombocytopenic Purpura. New England J. Med. **242**: 53 (Jan.), 1950.

The author reports the clinical course of a patient who developed thrombocytopenic purpura of the cerebral type following the administration of quinidine sulfate. The patient received 0.37 Gm. of quinidine sulfate at the onset of an attack of paroxysmal

auricular tachycardia and received an additional 0.2 Gm. after it has persisted for one hour. Recovery followed treatment with snake venom and several small transfusions. Further investigation revealed that a quinidine idiosyncrasy of this type had resulted on two previous occasions. Review of the literature emphasizes the rare occurrence of this specific type of sensitivity. The author was able to find only two previous reports of thrombocytopenia following quinidine administration.

NADLER

Talbott, J. H.: Use of Lithium Salts as a Substitute for Sodium Chloride. Arch. Int. Med. **85:** 1 (Jan.), 1950.

Human subjects were given lithium chloride experimentally to note its effects. The average daily consumption of lithium chloride was approximately 0.5 Gm. per person per day in patients with cardiac failure, hypertension or cirrhosis of the liver with ascites. A total of 14 normal persons ingested 1.56 Gm. of lithium carbonate daily which is approximately four times the determined average daily intake per person. In 6 subjects the serum lithium concentration was 0.5 mEq. per liter or less and in only 1 was it as high as 1.1 mEq. Some gastrointestinal irritability was noted in 6; correlation was observed between this symptom and the elevated serum lithium. The distress subsided after cessation of the intake. Three subjects experienced drowsiness. There were no symptoms reported at lithium levels below 0.7 mEq.

The hospital patients, under treatment for a variety of conditions, including diabetes mellitus, cardiac decompensation and chronic nephritis, received lithium carbonate tablets in quantities equivalent to 2.2 to 4.6 Gm. of lithium chloride daily. The longest period of forced ingestion in this series was nineteen days. Two patients complained of gastrointestinal irritability and 1 of depression, 1 of tremors, 1 of anorexia and tremors and 1 of gastrointestinal distress and tremors. In 4 of the 5 instances maximum serum lithium levels ranged from 2.3 mEq. to 3.9 mEq. per liter. Minimum serum sodium levels in these 5 patients ranged from 127.0 to 141.5 mEq. per liter. Untoward reactions were not found except in association with serum lithium concentrations above 1.0 mEq. per liter.

The incidence of valid reactions due to the ingestion of lithium is unknown. Reports of lithium intoxication which have appeared recently in the literature have been associated with the intake of surprisingly large amounts of lithium chloride. Sodium chloride deficiency per se or other factors, such as the presence of a debilitating disease, the administration of mercurial diuretics or digitalization, may be associated with many of the symptoms which have been attributed to lithium intoxication.

BERNSTEIN

Berris, B., and Aagaard, G. N.: Effect of Piperidylmethyl Benzodioxane on the Cold Pressor Response. Proc. Soc. Exper. Biol. & Med. **73:** 287 (Feb.), 1950.

This study was done to determine the effect of piperidylmethyl benzodioxane on the cold pressor response, in order to elucidate whether or not epinephrine is responsible for the rise in blood pressure on immersion of the hand in cold water. Piperidylmethyl benzodioxane did not block the cold pressor response in any of the patients studied. The lack of blocking suggests that the response is not due to the release of epinephrine since piperidylmethyl benzodioxane is said to have an adrenolytic action. The fact that cold stimulation causes a rise in both systolic and diastolic blood pressure also suggests that this response is on a neurogenic rather than an epinephrine-induced basis.

MINTZ

Mechelke, K. and Nusser, E.: Changes of Cardiac Dynamics Caused by Privine and Otrivine in Healthy Individuals. Arch. f. exper. Path. u. Pharmakol. **209:** 1 (Feb.), 1950.

The authors examined the action of Privine (2-naphthyl(1)-methylimidazolin) and of Otrivine (2-(beta-phenylethylamino)-imidazoline chlorhydrate) on 5 healthy medical students. Cardiac output was measured by the method of Broemser-Ranke. With the aid of simultaneous registration of carotid pulse, electrocardiogram and stethogram, the duration of mechanical systole and of the ejection period was measured. From these values the length of the isometric period was calculated. One half mg. of the drugs was injected intravenously. In all experiments the heart rate fell, the isometric period became prolonged, and the peripheral resistance was increased by 200 to 300 per cent. The cardiac output rose initially and diminished later with the increase of peripheral resistance. The ejection period was less prolonged than the presphygmic period.

SCHERF

Freis, E. D., Stanton, J. R., and Moister, F. C.: Assay in Man of the Chemical Fractions of Veratrum Viride, and Identification of the Pure Alkaloids Germitrine and Germidine as Potent Hypotensive Principles Derived from the Drug. J. Pharmacol. & Exper. Therap. **98:** 166 (Feb.), 1950.

In a study attempting to identify the hypotensive principle(s) of veratrum viride and, if possible, separate it from toxic principles responsible for side effects encountered in the use of the crude drug, several fractions of veratrum viride were given to a group of hypertensive patients. Since the previously known benzene-extractable alkaloids were found to be inactive, products obtained from the further purification of the residual amorphous fraction were studied. Fractions I and II were found to produce

hypotensive effects on both oral and intravenous administration. Germine, a crystalline alkaloid obtained by hydrolysis of these amorphous fractions, was inactive, but its two esters, germitrine and germidine, were active in doses of 1 and 3 mg., respectively. Moreover, germerine, a partial hydrolysis product of germitrine, was also active, though larger doses were required for comparable hypotensive action. The toxic side effects of the crude drug were encountered with all the above fractions.

GROSSMAN

Hafkenschiel, J. H., Crumpton, C. W. and Moyer, J. H.: The Effect of Intramuscular Dihydrocornine on the Cerebral Circulation in Normotensive Patients. J. Pharmacol. & Exper. Therap. **98**: 144 (Feb.), 1950.

In 5 normotensive subjects, cerebral blood flow and oxygen consumption were measured both prior to and following the intramuscular administration of 0.4 mg. of the adrenergic blocking drug, dihydrocornine. Despite a significant decrease in mean arterial blood pressure, the cerebral blood flow was maintained almost at control levels, indicating a decrease in cerebral vascular resistance. This effect was smaller than that encountered in hypertensive patients, presumably because of the greater control vascular resistance found in the latter. The decreased resistance in the present subjects was sufficient to prevent decrease in cerebral blood flow and to maintain normal oxygen uptake and undiminished oxygen content of the internal jugular vein.

GROSSMAN

Winsor, T.: Effects of SC 1950 (2,6-Dimethyl Diethyl Piperidinium Bromide) on Peripheral Circulation. Proc. Soc. Exper. Biol. & Med. **73**: 417 (March), 1950.

SC 1950 is a ganglionic blocking agent which in animal experiments has proved to be several times as potent as tetraethyl ammonium bromide. The author found that SC 1950 produces a fall in blood pressure in normal individuals as well as in patients with peripheral vascular disease, but in the latter group this response is subject to considerable variation. The fall in systolic pressure is greater than the fall in the diastolic pressure. The pulse rate is frequently elevated but considerable variations occur following the administration of SC 1950 intravenously. The pulse volume of the digits shows a marked increase in normal individuals, is somewhat less in patients with moderate peripheral arterial disease, and varies only insignificantly in patients with advanced organic peripheral arterial disease. The skin temperature of the digits rises sharply, often as much as 8 C. in normal individuals, while little change is observed in patients with advanced peripheral disease. Digital blood flow in normal individuals shows a marked increase, while it rises only slightly in patients with moderate or advanced peripheral arterial disease.

From these observations the author concludes, that SC 1950 is an effective spasmolytic agents capable of increasing the blood flow to the peripheral blood vessels, but it produces side reactions upon intravenous as well as rectal administration. The side reactions occurred in one-fourth of the subjects studied by the author. These responses included nasal obstruction, sighing respirations, weakness, nausea, dizziness, sleepiness, restlessness, angina, dry mouth, swelling of the throat, heavy eyelids, visual disturbances and thick speech.

MINTZ

PHYSICAL SIGNS

Lian, C. and Welti, J. J.: The Systolic Triple Rhythms. A Study of the Symptomatology. Reasons for Retention of the Term "Gallop Rhythm". Acta cardiol. **5**: 109, 1950.

The authors distinguish between two types of systolic triphasic rhythm according to the position of the additional sound in the heart cycle. The first type is protosystolic, the extra sound being superimposed on the second half of the first sound, sometimes producing a prolongation of the latter. When heard at the base, it usually has its origin in the pulmonary artery; when present over the apical region it can be ascribed to a pericardial vibration. The second type is meso- or telesystolic and is produced by an additional and distinct snap best heard between the xipoid process and apex. It is sometimes succeeded by a telesystolic murmur which is due to a momentary tension of a pleuropericardial adhesion. These types of systolic triple rhythm are different in genesis and meaning from a gallop rhythm. The latter term should be restricted to abnormal diastolic sounds caused by an irregular filling of a failing ventricle.

PICK

Miller, M., and Groedel, F. M.,: Esophageal Phonocardiography. Exper. Med. & Surg. **8**: 34 (Feb.), 1950.

The authors present phonocardiograms, taken at various levels inside the esophagus, from 1 noncardiac and 2 cardiac patients. In the noncardiac patient, the esophageal phonocardiogram revealed an auricular sound which was not present on the phonocardiogram taken from the chest wall. The phonocardiograms from the 2 cardiac patients showed a high-pitched, loud systolic murmur when taken from the chest wall and a softer, lower-pitched murmur when recorded in the esophagus. There was no auricular sound in any of the tracings from the 2 cardiac patients.

GELFAND

PHYSIOLOGY

Kobrak, E.: A Study of Tonus and Vascular Tonus with Special Reference to Circulatory Problems. Ztschr. f.d.ges. inn. Med. **4**: 577 (Oct.), 1949.

Tonus is a quality of contractile, living substance which becomes apparent in the form of resistance against forces which produce tension or which have a general tendency to produce dislocation. In contrast to elasticity, also found in nonliving substrates like caoutchouc, resistance due to tonus is variable and is controlled by hormonal and nervous influences, the latter originating either centrally in the hypo[illegible]mus or in the periphery. Variations in tonus are acco[illegible]panied by variations in turgor, irritability and reactivity, and, in the capillary system, by changes of secretion and transudation.

To measure the tonus of skin arterioles in man, suction was applied to a limited area of the chest and the hyperemic reaction following different degrees of negative pressure—measured by a manometer—was compared in normal and abnormal individuals. The authors observed three types of abnormal response. The first, indicating a constantly increased tonus, was found in persons with a tendency to "spasticity" (ulcus ventriculi, migraine). A second type, showing great variations of the reaction, was found in women during the menopause and in patients with a marked lability of the blood pressure and other vasomotor reactions. The third group with constantly and abnormally low tonus of the skin vessels consisted mainly of patients with signs of hyperactivity of the thyroid gland.

PICK

Binet, L., and Burstein, M.: Demonstration of a Vasoconstrictive Factor in the Arterial Blood of the Dog following Centripetal Stimulation of the Vagus Nerve. Compt. rend. Soc. de biol. **143**: 1344 (Oct.), 1949.

The authors perfused the denervated hind leg of a dog with arterial blood of another dog. If in the latter animal the proximal end of the vagus was stimulated faradically, a rise in blood pressure occurred not only in the donor animal but also in the perfused leg of the receptor animal. A synthetic sympatholytic drug (883 F) did not prevent this phenomenon. The authors conclude that the vasoconstrictive substance appearing in the blood following vagus stimulation is not identical with epinephrine.

PICK

Binet, L., and Burstein M.: Passage into the Blood of a Vasoconstrictive Substance of Cerebral Origin following Centripetal Stimulation of the Vagus in the Dog. Compt. rend. Soc.de biol. **143**: 1347 (Oct.), 1949.

If the denervated hind leg of a dog is perfused with venous blood from the jugular veins of another dog, a rise of blood pressure in the perfused leg of the receptor animal can be noted following faradic stimulation of the central end of the vagus of the donor animal. The effective vascoconstrictive substance appearing in the blood following stimulation of the vagus is a cerebral origin and is probably produced in the posterior lobe of the hypophysis.

PICK

Williamson, B.: Diastole. Edinburgh M. J. **56**: 601 (Dec.), 1949.

The importance of diastole in the cardiac cycle is emphasized. Diastole is not a negative phase and is considered the more important phase of the cardiac cycle since it decides the welfare of the myocardium itself. Tachycardia, which shortens diastole more than systole, should be controlled in order to give the myocardium better circulation. Distinction between the tachycardia which is compensatory to a loss in myocardial force and that which results from extracardiac demands must be made in all cases. The apnea test will cause an increase in heart rate where there is a loss of myocardial force in the absence of increased metabolic rate. In extrinsic tachycardia with sympathetic excess (not accompanied by an increase in metabolism as found in hyperthyroidism or febrile states), the induction of apnea usually produces a pronounced slowing action through the vagus.

The heart slows overnight because of the influence of the vagus. Thus diastole is prolonged. The blood pressure falls with the slowing of the pulse and if arteriosclerosis is added a triad is present which accounts for the nocturnal incidence of thromboses, both cerebral and coronary. The author suggests the use of whisky as a night cap to raise the metabolism. Thyroid an hour or so before sleep may serve the same purpose. Adrenaline solution as a solvent for atropine, a vagal inhibitor, and strychnine, a central stimulant, may be used. Simple vagotonia may be counteracted by belladonna, caffeine or Benzedrine.

GELFAND

RHEUMATIC FEVER

Clemmesen, S.: Rheumatic Fever Statistics in Denmark from 1878 to 1946 and their Significance in Prophylaxis. Acta med. Scandinav. **136**: (Suppl. 234) 109, 1949.

Reliable data concerning the incidence of rheumatic fever and sore throat in Denmark since 1878 is available. The incidence of rheumatic fever at all ages has decreased through the years. The incidence now is so low that the question of prophylaxis has not arisen. The peaks of curves of sore throat and rheumatic fever correspond and suggest epidemics produced by hemolytic streptococci. However, the total curve of the incidence of rheumatic fever is

falling while that for pharyngitis is rising. This suggests that most cases of pharyngitis today are caused by agents that do not cause rheumatic fever or else that over predisposing and precipitating factors play a role in determining the incidence of rheumatic fever.

WAIFE

Wasson, V. P., Miley, G. P., and Dunning, P. M.: Ultraviolet Blood Irradiation Therapy (Knott Technique) in Rheumatic Fever in Children. Exper. Med. & Surg. **8:** 15 (Feb.), 1950.

From 22 hospitalized children with acute rheumatic carditis and 86 outpatient children with acute or subacute rheumatic fever with or without carditis, 1.5 cc. of blood per pound of body weight were removed, citrated and exposed to ultraviolet light and returned to the same vein. This procedure was repeated weekly, then biweekly and then at gradually increasing intervals. A rapid subsidence of all toxic symptoms occurred in 20 of 22 children; the average time for subsidence was 3 to 4 days. Definite cardiac improvement was noted in all, cardiac murmurs became less audible or disappeared, and the exercise tolerance became normal. Only one recurrence of the rheumatic state was noted in the 2 to 4 year follow-up study. Only 2 recurrences (0.8 per cent) developed in 107 cases of rheumatic fever which received ultraviolet irradiation prophylactically and which were followed for 2 to 4 years, during which time no other prophylactic treatment was given.

WAIFE

Fjellman, A. A.: Rheumatic Fever in the Aged. Nord. med. **3:** 381 (March), 1950.

The total number of patients hospitalized since January 1942 in Vasa Hospital, Gothenburg, was 14,700. Senile rheumatic fever was diagnosed in one patient only. This patient was a 75 year old man who developed rheumatoid arthritis which, after a period of relief, recurred. The course, sedimentation rate, antistreptolysin titer, and electrocardiogram showed changes typical of rheumatic fever with acute carditis. After 11 weeks hospitalization the patient was discharged free from symptoms and signs.

AUTHORS

ROENTGENOLOGY

Anderson, T.: A Design for an Electrokymograph and Some Fundamental Considerations on the Electrokymogram. Acta radiol. **32:** 276, 1949.

The filtering of interfering frequencies in the existing types of electrokymographic apparatus imposes its own frequencies which approach the frequency band that it is desirable to record. Since certain phases of the heart cycle to be recorded are extremely rapid, these filter frequencies may interfere with the shape of the resulting curves. Four common types of interferences may be present: those associated with the photomultiplier tube working at 1000 volts or more, with main line fluctuations, or with ripple frequencies due to valve tube rectification, and interference from outside power sources.

The author describes two electrokymographic channels built into one machine with the interfering frequencies mentioned above either eliminated or modified insofar as possible. These electrokymograms are fed into a four channel photographic recording device, making possible the additional recording of two electrocardiograms or one sphygmogram plus one lead of an electrocardiogram. Carotid sphygmography is accomplished by means of a piezoelectric pickup unit so that no appreciable time lag appears in the recording system. Time relationships with the electrocardiogram are not regarded as being precise enough. The relationship of heart contour motion to changes in density of the part of the heart covered by the slit is discussed. The author concludes that an appreciable but variable portion of the recorded curve is due to differences in density.

SCHWEDEL

Ducuing, J., Pons, H., and Enjalbert, A.: Abdominal Aortography. J. de radiol. et d'electrol. **30:** 497. 1949.

The authors quote Dos Santos who states that over 3,000 aortographies have been performed without serious sequelae. Under general anesthesia, a needle 12 cm. or longer is directed anteriorly and medially to the left of D1 and D2 until the abdominal aorta is entered. Ten to twelve cc. of the organic iodine dye is then injected and appropriate roentgenograms taken. The injection may be repeated. This procedure is useful in visualizing disease of the abdominal aorta itself and of some of its main branches. Adjacent tumor masses may be differentiated from aneurysms. The cause for diminished arterial circulation to the extremities can be determined.

SCHWEDEL

SURGERY IN HEART AND VASCULAR SYSTEM

Donovan, T. J.: The Uses of Plastic Tubes in the Reparative Surgery of Battle Injuries to Arteries with and without Intra-arterial Heparin Administration. Ann. Surg. **130:** 1024 (Dec.), 1949.

Polyethylene tubes were used to bridge gaps in the thoracic aorta of dogs, in order to determine the bodily reactions to this type of procedure. Several of the animals died of aortic rupture while others lived up to one year after the operation. Anastomosis of the femoral artery was performed, using both polyethylene and lucite tubes. However, the average duration of patency was only two days for the polyethylene and three days for the lucite tubes. Soakin

the tubes preoperatively with heparin did not affect the tendency to thrombosis. Comparison of the results obtained with the tubes with those results following arterial ligation revealed that an adequate collateral circulation developed in the case of the former procedure, while after ligation, the limb was generally quite ischemic for the next twenty-four hours. Intra-arterial administration of heparin appeared to prolong the period of patency of the vessel without causing a significant prolongation of the systemic clotting time.

ABRAMSON

Callow, A. D., and Welch, C. S.: Arterial Anastomosis in Experimental Arterial Injury. Surg., Gynec. & Obst. 90: 77 (Jan.), 1950.

Because of the very high percentage of cases requiring amputation after ligation of femoral and popliteal arteries in the treatment of arterial injury, the authors carried out an experimental study on dogs of the various methods currently used for reuniting severed vessels. It was found that arterial reunion by end-to-end suture, arterial hemograft bridge and nonsuture vein graft produced a successful result, provided the operation was performed in a clean wound immediately after arterial severance. The use of plastic tubing or other inert materials was not as satisfactory.

ABRAMSON

Young, R. L., and Derbyshire, R. C.: Ligation of the Inferior Vena Cava During Pregnancy. Ann. Surg. 131: 252 (Feb.), 1950.

This report deals with a patient in the early stage of pregnancy in whom the inferior vena cava was ligated as treatment for phlebothrombosis. Despite the procedure, no difficulty was encountered with regard to the pregnant state, and at the anticipated time a normal infant was born. The authors are of the opinion that during pregnancy the use of anticoagulants in the treatment of venous thrombosis is hazardous, and, therefore, vein interruption, with extraction of the clot distal to the site of ligation, is the method of choice. Postoperative sympathetic blocks are of value in minimizing complications and in overcoming reflex spasm.

ABRAMSON

Albright, H. L., and Leonard, F. C.: Embolectomy from the Abdominal Aorta. New England J. Med. 242: 271 (Feb.), 1950.

The authors review 25 previously reported cases in which aortic embolectomy was performed and add a detailed description of a twenty-sixth case in a 65 year old woman with an embolism of the left popliteal region. Heparin and dicumarol were administered, and left lumbar sympathetic block with Novocain was carried out. On the second day, the patient developed diagnostic signs of embolism of the aorta, and within one and one-half hours of the acute episode, embolectomy was performed. The embolus was removed through an anterior incision in the aorta. Recovery followed.

The authors conclude that embolectomy is the choice treatment in saddle emboli. This is to be combined with or followed by conservative measures such as anticoagulants and lumbar sympathetic blocks. They also believe that immediate operation yields results that are more successful than those obtained when a period of time elapses between occlusion and operation.

NADLER

THROMBOEMBOLIC PHENOMENA

Harvey, W. P., and Finch, C. A.: Dicumarol Prophylaxis of Thromboembolic Disease in Congestive Heart Failure. New England J. Med. 242: 208 (Feb.), 1950.

Because of bed confinement, stasis of blood in dependent edematous legs, and perhaps damage to venous endothelium from pressure and anoxia, patients with congestive heart failure are liable to thromboembolic phenomena. The authors, therefore, studied the effectiveness of dicumarol in preventing such complication in these individuals. An attempt was made to maintain prothrombin time at approximately 30 per cent. In the control group of 100 patients there were 13 pulmonary emboli and 8 cases of thrombophlebitis, while in the dicumarol-treated group of 80 patients there were 2 questionable cases of pulmonary embolism and 1 definite and 1 questionable case of thrombophlebitis. As a probable result of pulmonary embolism, 8 patients in the control group died, as compared with none in the dicumarol-treated group.

It was concluded that in patients hospitalized with congestive heart disease, dicumarol therapy results in a significant reduction in thromboembolic disease and hence in the mortality in such a group.

ABRAMSON

McCann, J. C.: Thromboembolism. A Comparison of the Effect of Early Postoperative Ambulation and Dicumarol on its Incidence. New England J. Med. 242: 203 (Feb.), 1950.

The author studied the effect of various types of postoperative regimens on the incidence of thromboembolism. In one series of 674 patients, the traditional 10 day period of bed rest was used, and in this group there were 18 cases of thrombotic complications (2.7 per cent). In 85 per cent of the second series of 640 cases, ambulation was permitted on the first to the third postoperative day, and at the same time care was taken to prevent pressure on the calf muscles in these patients, their extremities were kept in the elevated position while resting, and they all received small doses of epinephrine in oil, in order to stimulate the circulation. Despite all these measures, 15 thrombotic complications occurred (2.3 per cent). In 95 per cent of a third series of 504 patients,

ambulation was delayed to the third to the seventh day, and in this group 12 cases of thromboembolism (2.3 per cent) were encountered. Sixty per cent of the failures after early ambulation occurred in patients past 50 years of age. When dicumarol was administered prophylactically to all patients not permitted ambulation on the first to the third day, the rate of thromboembolism dropped to 1.5 per cent. A prophylactic level of 40 to 50 per cent prothrombin index was obtained in each case, and at this range no significant bleeding was encountered.

ABRAMSON

Schenken, J. R., Slaughter, G. P., and De May, G. H.: Maternal Pulmonary Embolism of Amniotic Fluid. Am. J. Clin. Path. **20:** 147 (Feb.), 1950.

The authors add another to the 16 cases of embolism of amniotic fluid reported in the literature. During the course of labor, the patient suddenly developed marked cyanosis, air hunger and shock and then expired. At autopsy the pulmonary vessels were found to contain debris of amniotic fluid, and an intense local inflammatory reaction was noted. On the basis of an analysis of the cases in the literature, the authors conclude that a number of factors contribute to the pathogenesis of the condition, namely, entrapped amniotic fluid containing considerable debris, a rent in the fetal membranes, and uterine contractions of sufficient force to overcome the venous pressure in the open venous sinuses.

ABRAMSON

Andrus, W. D.: Peripheral Arterial Embolism. With Particular Reference to an Evaluation of Conservative Treatment. Arch. Surg. **60:** 511 (March), 1950.

On the basis of a study of 72 instances of embolism of the main vessels of the upper and lower extremities, the authors came to certain conclusions regarding the type of therapy to be used under various circumstances. In the case of an embolus of the saddle type or one involving either or both iliac arteries, there appears to be little question that for the patients who can tolerate the operation, embolectomy is indicated. For embolism at all other locations conservative measures have produced as low a mortality rate as that reported in series in which embolectomy was performed. These conservative procedures consist of anticoagulant therapy and means aimed at the relief of spasm in the vessels of the extremity, including paravertebral sympathetic blocks, sympathectomy and papaverine. However, since the conservative approach is frequently followed by signs of a reduced circulation, such as intermittent claudication, embolectomy should be attempted in patients of the younger age group, provided the condition is recognized within 12 hours of its inception and the embolism is secondary to old rheumatic heart disease in the absence of congestive heart failure. For the elderly patient with generalized arteriosclerosis involving the heart, the chances of improving the situation by adding embolectomy to the conservative measures now available are so small as to contraindicate its use except in rare cases.

ABRAMSON

Pierce, F. R., and Domenici, T. J.: Problems and Practices in a Community Hospitals. I. Treatment of Venous Thrombosis. New England J. Med. **242:** 395 (March), 1950.

The authors review the various therapeutic approaches to the problem of venous thrombosis as observed in a small general hospital. They point out that although early ambulation should theoretically be a desirable prophylactic measure, statistically there is no real evidence that this procedure reduces thrombotic episodes. Attention is called to the belief that anticoagulant therapy and venous interruption are not competitive methods of treatment and that one need not be chosen to the exclusion of the other; they should be used singly or in combination, as required.

Anticoagulants have been proved to be an effective tool in the treatment of venous thrombosis. They should be continued until almost complete regression of swelling of the involved extremity has occurred in the case of deep thrombophlebitis and until tenderness and the Homans' sign have disappeared in the case of phlebothrombosis. When pulmonary embolism exists, dicumarol is discontinued only after signs of consolidation in the chest are no longer present, when the sputum is no longer blood-tinged and the temperature, pulse and respiration have returned to normal. In the elderly patient the prophylactic measure of choice is venous interruption rather than anticoagulant therapy. This rule also holds for the antepartum patient in whom venous thrombosis is suspected, since dicumarol passes through the placenta and hence may have a deleterious effect on the fetus.

ABRAMSON

VASCULAR DISEASE

Denolin, H., Lequime, J., and Jonnart, L.: Arteriovenous Pulmonary Aneurysm. A Physiopathologic Study. Acta. cardiol. **5:** 144, 1950.

The authors report the case of a 19 year old male patient who, since the age of 15 years, had had progressive dyspnea, cyanosis and clubbing. The physical examination of the heart and the electrocardiogram was normal. At the base of the left lung a double murmur was heard and at x-ray examination a pear-shaped shadow with pulsation in the vertical direction was found adjacent to the left hilus The oxygen saturation of the arterial blood was 85 per cent; the cardiac output, determined by Fick's method, was 6.87 liters per minute, 3.12 liters (45 per cent) of which were calculated to be shunted to the pulmonary veins, at the site of a pulmonary

aneurysm. During an exercise test there was a decrease of the oxygen utilization (ratio of oxygen consumption and pulmonary ventilation) and further decrease in oxygen saturation of the arterial blood. The changes following exercise are explained by an increase of the amount of blood shunted from the pulmonary artery to the pulmonary veins.

PICK

Lequime, J., Denolin, H., Delcourt, R., Verniory, A., and Callebaut, C.: Arteriovenous Aneurysm in Osler's Hemorrhagic Teleangiectasia. Acta. cardiol. **5**: 63, 1950.

The authors report the case of a 65 year old woman with multiple pulmonary aneurysms accompanied by cyanosis, polycythemia, and clubbing of the extremities of 45 years' duration. Ether circulation times suggested a venoarterial shunt by the appearance of tingling in the face. Gas analyses and catheterization data suggested marked arterial unsaturation and a widely patent right to left shunt (89 per cent according to the formula of Lundsgaard and Van Slyke. An autopsy confirmed the clinical findings.

HECHT

Segers, M., Regnier, M., and Denolin, H.: Pulsating Lung Tumor with an Arteriovenous Shunt. Acta. cardiol. **5**: 156, 1950.

The authors report the case of a 63 year old woman with slight cyanosis which had been persistent for 15 years without signs of heart disease. At fluoroscopy a shadow was seen in the region of the left hilum and pulsation of its upper border was studied by kymography. Expansion of the tumor occurred at the time of ventricular contraction. An electrokymogram, registered simultaneously with the electrocardiogram, revealed that this pulsation occurred earlier (0.04 second) after the onset of the QRS than the usual pulsation of the pulmonary artery (0.08 to 0.14 second). This abnormally early ejection of the right ventricle is ascribed to low pulmonary pressure due to the presence of an arteriovenous shunt within the pulmonary circulation. The magnitude of the shunt was calculated by the authors from the oxygen saturation in peripheral arterial and venous blood and was found to be approximately 18 per cent.

PICK

Wartman, W. B.: Hemorrhage into the Arterial Wall as a Cause of Peripheral Vascular Disease. Am. Heart J. **39**: 79 (Jan.), 1950.

The author describes the pathologic changes observed in the arteries of the lower extremities of 3 patients with obstructive arteriosclerosis. Extensive vascularization of the arterial wall was noted; this was associated with bleeding and the formation of large hematomas with obstruction of the lumen by pressure or rupture and thrombosis. The lesions were similar to those described in cases of arteriosclerosis of coronary, pulmonary, cerebral, carotid and renal arteries. It is concluded that the presence of arterial disease of the legs may be an indication of more serious vascular lesions elsewhere, especially in the heart.

ABRAMSON

Ruben, J. E.: Continuous Lumbar Sympathetic Block for the Treatment of Acute Arterial Occlusion and other Vascular Diseases of the Lower Extremity. Ann. Surg. **131**: 194 (Feb.), 1950.

The effect of continuous lumbar sympathetic block was studied in 48 patients with various peripheral vascular disorders of the lower extremities. The technic consisted of inserting a spinal catheter into the epidural space through the sacral hiatus and connecting it to a flask containing 1000 cc. of 0.1 per cent procaine solution. The anesthetic reached the communicating rami in the peridural space through gravity. The treatment was maintained for a minimum of 24 hours.

Of the 10 patients in the series suffering from sudden occlusion of a major artery, in 2, sufficient collateral circulation developed to preserve the limb, while in the remaining cases either gangrene occurred or the patient died of other causes. Seven cases with chronic arterial vascular diseases were treated with continuous blocks and the results were encouraging in that rest pain was reduced during the period of therapy. Twelve of 18 patients in the acute stage of deep thrombophlebitis became clinically well during the procedure or almost immediately after the continuous block was stopped. According to the authors, the method described by them gives better results than those obtainable with other means of producing lumbar sympathetic block.

ABRAMSON

Strohl, E. L., and Lasner, J.: Mesenteric Vascular Occlusion. Arch. Surg. **60**: 339 (Feb.), 1950.

The authors present another instance of survival after resection for mesenteric vascular occlusion, bringing the number of such cases reported in the literature up to sixty-three. The symptoms in this patient at the time of hospitalization consisted of generalized and continuous abdominal pain of seven days' duration. This pain was not related to the intake of food or liquids, it did not radiate, nor was it associated with nausea, vomiting, tenderness or distention. Bowel movements had been normal in color and consistency and occurred once daily. Five days after the patient was admitted to the hospital, severe and excruciating pain was experienced in the lower left region of the abdomen. The abdomen became tense and tender and no peristaltic sounds could now be heard. At time of operation a gangrenous loop of ileum was found. This was resected and an end-to-end anastomosis was performed. The pathologic report was mesenteric vein thrombosis and hemorrhagic necrosis of the small bowel.

ABRAMSON

Scheinberg, P.: Cerebral Blood Flow in Vascular Disease of the Brain. With Observations on the Effect of Stellate Ganglion Block. Am. J. Med. **8:** 139 (Feb.), 1950.

Utilizing the nitrous oxide technic of Kety and Schmidt the author made a study of the cerebral blood flow per 100 grams of brain, the arteriovenous oxygen difference, the arteriovenous glucose difference, cerebral oxygen utilization, cerebral glucose utilization and cerebrovascular resistance in 23 patients who were either middle-aged individuals with hypertension and diabetes or individuals with a history of a cerebral vascular accident. Those in this group with normal mental status had lower cerebral blood flows, higher arteriovenous oxygen differences and higher cerebral-vascular resistances than normal young persons but cerebral oxygen and glucose utilizations were normal. Those with abnormal mental status had lower cerebral blood flows, lower cerebral oxygen and glucose utilizations and higher cerebrovascular resistances than those with normal mental status or than normal young subjects. The author believes that these groups represent two stages in the natural progression of cerebral vascular disease.

Unilateral stellate ganglion block produced no change in cerebral vascular function in normals, in patients with hypertensive vascular disease or in elderly patients with cerebral thrombosis. The decrease in cerebral function is related to the inability of the brain to extract more oxygen and glucose per unit of blood rather than to the blood flow itself. This metabolic defect is probably related to the greatly increased resistance offered to the flow of blood by the diseased cerebral vessels. The failure of the cerebral blood flow to increase in these patients following stellate ganglion block would indicate that the increased cerebrovascular resistance is not due to increased tone mediated by the sympathetic nervous system.

LEVINE

King, B. G.: The Clinical Diagnosis of Periarteritis Nodosa. Report of Four Cases. Ann. Int. Med. **32:** 466 (March), 1950.

The diagnosis of periarteritis nodosa was suspected during life in 4 young adult males and confirmed by examination of necropsy material in 3 cases and by biopsy of a gastrocnemius muscle in the fourth case. There were no allergic manifestations in any of the cases and no precipitating cause was evident. Eosinophilia in the blood was a conspicuous feature in only 1 of the cases. Clinical evidence of renal disease was present in 3 of the 4 cases. A striking finding in all cases was the involvement of the nervous system. This consisted of fleeting paresis of one or more extremities, or daily variations in the deep tendon reflexes (a prominent feature in all cases) and a marked swelling of the optic nerve (in one case). Ulceration of the gastrointestinal tract occurred in 3 of the 4 patients as a result of periarteritis involving the arteries nourishing the wall of the stomach and duodenum. Clinical evidences of cardiac involvement, such as a pericardial friction rub, gallop rhythm, and electrocardiographic changes, were present in all of them. Fleeting subcutaneous nodules, skin rashes, joint swellings, and varying degrees of fever were also characteristic findings. The clinical and postmortem findings in these cases support the conclusions of other observers that the organs most involved in cases of periarteritis nodosa are the kidneys, heart, liver, gastrointestinal tract, mesenteric vessels, muscles, spleen, lungs, and the central and peripheral nervous system. The protean clinical manifestations in this disease are to be explained on such widespread involvement of tissues in various parts of the body.

WENDKOS

Soave, F.: Pneumonectomy in a Case of Fistula Between the Middle Lobe Bronchus and Middle Lobe Artery. Thorax **5:** 90 (March), 1950.

The author presents the unique case of a patient treated by pneumonectomy for a fistula between the right middle lobe bronchus and the artery to the right middle lobe. The patient was a 48 year old man with a history of repeated bouts of hemoptysis over a period of 24 years. He had been subjected to repeated bronchoscopies with biopsies reported as "bronchial tuberculosis". At the time of admission just before operation x-ray study of the chest showed that the right diaphragm was slightly elevated. A well defined shadow which had the appearance of parenchymatous thickening was present in the hilar zone in the posteroanterior view. In the lateral projection this thickening was evidently due to a partial atelectasis of the middle lobe. The right lung was removed and examination showed a small hole about 4 mm. in diameter in the distal part of the angle formed by the main bronchus and the middle lobe bronchus. This hole communicated directly with the pulmonary artery. Around the fistula were the remains of a lymph node. An intense chronic inflammation surrounded the fistula. It was assumed that there had been a tuberculous abscess of a lymph node with gradual erosion of both bronchial and arterial walls in the vicinity of the node, resulting in a communication between the two.

KLOSK

Starkloff, G. B., Bricker, E. M., McDonald, J. J., and Litzow, L. T.: Proximal Femoral Venography. Ann. Surg. **131:** 413 (March), 1950.

The authors present a new technic for visualizing the deep venous system by means of venography. Under local anesthesia, the saphenous vein is sectioned and its distal end and its tributaries are ligated. A ureteral catheter is inserted into the proximal end and the vein is tied around it. With the patient standing, diodrast is injected through the

catheter and several x-rays films are taken in succession over a period of four minutes. Through such a procedure information can be obtained which should be a valuable supplement to the other methods of determining the cause of chronic venous insufficiency of the lower extremity. Delay in emptying and retrograde flow of the contrast medium in the upright position are findings considered to be of significance.

ABRAMSON

Naide, N.: Diphenhydramine (Benadryl) for Nocturnal Leg Cramps. J.A.M.A. **142:** 1140 (April), 1950.

The author used benadryl hydrochloride, 50 mg. at bedtime, in a series of 17 patients with night cramps and obtained prompt relief in all instances. The mechanism by which the drug relieves this condition is not known.

ABRAMSON

Friedell, M. T., Indeck, W., and Schaffner, F.: Radioactive Isotopes in the Study of Peripheral Vascular Disease. Arch. Int. Med. **85:** 667 (April), 1950.

The use of a radioactive isotope (P^{32}) in determining the status of the peripheral arterial circulation was studied. The reciprocal rate of deposition as plotted on a semilogarithmic curve was designated as the circulatory index. The author found that the change in the index produced by vasodilatation can be used as a guide to selected therapy. Four main groups representing types of response were noted. It was concluded that Priscoline (2-benzylimidazoline hydrochloride) when administered intravenously will alter the circulatory index as determined with radioactive phosphorus. The prognosis of the groups as determined with Priscoline coincides with that of groups determined by other vasodilating mechanisms. Priscoline is apparently more effective in conditions primarily due to interference with the blood supply. It is less effective in severe associated causalgic states. Orally administered Priscoline is useful in the management of certain disorders of the peripheral vascular system.

BERNSTEIN

Berman, L. G., and Russo, F. R.: Abdominal Angina. New England J. Med. **242:** 611 (April), 1950.

The authors review the literature and present case reports of 2 patients with abdominal angina due to thrombosis of the smaller mesenteric blood vessels. Typically generalized arteriosclerosis was present, together with hypertension in one case. Both had a history of crampy abdominal pain following large meals. Laporatomy revealed a healed infarct of the jejunum in one patient and actual gangrene of this segment of bowel in another. Only when thrombosis and infarction occurred were localizing abdominal signs present. Considering the effect of a large meal on the intestine as being analogous to the effect of exercise on coronary artery disease, the authors compare abdominal angina with angina pectoris.

NADLER

Stone, P. W., and Cooper, F. W., Jr.: Treatment of Experimental Acute Arterial Insufficiency. A Comparison of the Sympatholytic Agent Priscoline (2 Benzyl-4,5-imidazoline HCl) and Sympathectomy. Surgery **27:** 572 (April), 1950.

The authors studied the vasodilating effects of Priscoline and sympathectomy on the limbs of 30 dogs in which the circulation was reduced to a critical level through excision of the aortic trifurcation and division of the deep circumflex iliac artery. On the basis of the results, the authors concluded that the administration of a drug like Priscoline in a dosage designed to produce constant sympatholysis is not only ineffectual but is actually deleterious when given to an animal suffering from profound arterial insufficiency. However, if administered so as to produce an intermittent rather than a constant vasodilatation, the therapeutic efficiency of the drug may be enhanced. Lumbar sympathectomy is of limited value in this regard.

ABRAMSON

Wright, H. P., Osborn, S. B., and Edmonds, D. G.: Changes in the Rate of Flow of Venous Blood in the Leg during Pregnancy, Measured with Radioactive Sodium. Surg., Gynec. & Obst. **90:** 481 (April), 1950.

The rate of flow of venous blood in the leg was studied in 61 normal pregnant women by means of radioactive sodium. As pregnancy advanced, the readings, which were normal in the early stage, indicated a slowing of flow. The increase in foot to groin time was fairly gradual and constant, but it seemed possible that the engagement of the fetal head might cause a secondary obstruction to blood flow. Comparison of arm flows showed no significant change in the upper extremity.

It is suggested that the slowing in venous flow in the legs of pregnant women is brought about by an increase in intra-abdominal pressure associated with the changes going on in the uterus. This slowing may be a factor in the onset of venous thrombosis.

ABRAMSON

OTHER SUBJECTS

Coelho, E.: Cardiac Changes in the Severe Suprarenal Insufficiency. Annual meeting Swedish Soc. Cardiol., Stockholm, Sept. 24–25, 1949, Lisbon, Bertrand LDA, 1950.

The author studied cardiac changes in severe cases of adrenal insufficiency. Following the crisis of Addison's disease, cardiac enlargement with increase of both the long and the broad diameter of

the heart was found by x-ray study. The enlargement persisted when electrolytic balance was reestablished and was not influenced by treatment. Coincident with this, the following electrocardiographic changes frequently occurred: increased duration of Q-T, depression of S-T and inversion of T waves. These changes disappeared if treatment with adrenocortical hormone, sodium chloride, and ascorbic acid succeeded in overcoming the Addison crisis. If treatment was unsuccessful, however, the electrocardiographic changes persisted. All patients who presented persistent changes of the electrocardiogram died within a short period. The electrocardiographic changes result, according to the author, from changes in electrolyte metabolism, decreased amount of glycogen in the heart muscle, and increase of both potassium and lactic acid in the blood.

LUISADA

Humphrey, J. H.: The Nature of Antistreptolysin S in the Sera of Man and of Other Species. The Lipoprotein Properties of Antistreptolysin S. Brit. J. Exper. Path. **30**: 365 (Oct.), 1949.

Experimental evidence is presented to support the thesis that antistreptolysin S is not an antibody in the accepted sense, and that its nature varies among species and even among individuals. Treatment of the sera of man, horse, rabbit, rat, ox and sheep with ether or alcohol-ether in such a manner as to cause only minor changes in the titers of known antibiodies, causes a major reduction in antistreptolysin titer. This phenomenon is less marked in guinea-pig serum.

In human serum most of the antistreptolysin S activity is carried by a labile lipoprotein complex associated with the albumen fraction, but the globulin fractions also have some activity, most of which is retained after gentle treatment with fat solvents. Mild denaturation or peptic digestion may increase the antistreptolysin S activity by loosening the lipoprotein complexes without destroying that part of the proteins which carries the residual antistreptolysin S activity after ether extraction. More extensive digestion of the proteins destroys this residual, antistreptolysin S. Similar findings were also noted in horse serum, although in some specimens a large amount of active lipoprotein complex may be found in the euglobulin fraction. In guinea-pig serum lipoprotein complexes are either unimportant in this connection or are so stable that they are unaffected by treatment with ether.

It is possible that the widespread occurrence of antistreptolysin S may account for the apparent unimportance of streptolysin S production in determining the virulence of streptococci.

SCHWARTZ

Ruf, F., Roesch, H., and Walz, L.: The Healthy and Diseased Heart in Surgical Diseases of the Upper Abdomen. Ztschr. f. Kreislaufforsch **38**: 641 (Nov.), 1949.

The authors report electrocardiographic observations on 23 patients with cholecystopathy and 15 patients with ulcus ventriculi before, during, and after operation. The preoperative electrocardiogram was found to be abnormal, as judged by S-T depressions, in a high percentage of persons with gall bladder disease. Changes ascribed to the psychic trauma connected with the operation and changes occurring during anesthesia were noted in both groups. In patients with gall bladder disease, the latter changes consisted often in the appearance of an ectopic nodal rhythm with A-V dissociation. Premature beats were found only occasionally. During the operation an increase of heart rate was observed in both groups and was maximal during manipulation of the diseased organ. Pre-existent RS-T depressions became more marked during this phase. In the ulcer patients, splanchnic anesthesia was followed by a drop in heart rate and an increase of the amplitude of P and T waves.

In a number of patients with cholecystopathy an improvement of the abnormal electrocardiogram was noted following operation. This suggests a causal connection between gall bladder disease and the myocardial damage manifested in the electrocardiogram. The latter finding in a patient with chronic cholecystopathy should, therefore, be considered as an absolute indication, and not as a contraindication, for a cholecystectomy.

PICK

Bustamente, R., and Perez-Stable, E.: Pericardial Effusion in Myxedema Heart. Rev. cubana de cardiol. **10**: 205 (Oct.–Dec.), 1949.

The authors report 5 cases of pericardial effusion in "myxedema heart." The cardiac area was considerably increased in 2 and moderately increased in 3 cases. Fluid was aspirated in all of them. This fact and the similarity in clinical, x-ray and electrocardiographic findings in pericardial effusion in general and in the myxedema heart lend support to the belief that in this condition there is always fluid present in the pericardial cavity if the heart shadow is enlarged, the part played by the fluid in the enlargement being greater the more pronounced the enlargement. The electrocardiographic changes persisted in 1 case after the fluid was withdrawn and the cardiac shadow had returned to normal, which indicates that these changes are not caused by the fluid alone. The fluid contained from 0.84 to 6.15 per cent protein; cholesterol was present in all cases, but in quantities much below the blood level (15.6 and 18.7 mg. per cent in 2 instances). The authors conclude that evacuation of the pericardial fluid by aspiration seems indicated as a therapeutic measure and may shorten the period of regression of the cardiac enlargement.

ULLMANN

Vander Veer, J. B., and Kuo, P. T.: Cardiac Disease in Pregnancy. A Study of the Patients with Heart Disease at the Philadelphia Lying-In Division of the Pennsylvania Hospital from 1937 to 1947, Inclusive. Am. Heart J. **39**: 2 (Jan.), 1950.

Heart disease of some type was found in 409 (1.5 per cent) of a total of 26,628 pregnant women delivered during an 11 year period of study. The maternal mortality rate among the cardiac patients was 3.4 per cent (14 deaths). Congestive heart failure was the main or contributory cause of death in 10 of these patients, and fatal acute infections were present in 7. Prematurity was the most common cause of the 54 fetal deaths, making a mortality rate of 13.2 per cent. Of the 409 patients studied, there were 324 with rheumatic heart disease, of whom 11 died; 51 patients had hypertensive cardiovascular disease; and 18 patients had congenital defects, one of whom died. There were 2 additional maternal deaths due to acute bacterial endocarditis.

A definite diagnosis of cardiac disease is often difficult during pregnancy. Symptoms and signs simulating early myocardial insufficiency may occur late in pregnancy in women with no organic heart disease. However, early evidence of heart failure may become manifest by elevation of the respiratory rate, tachycardia, and the appearance of moist rales at the lung bases.

Patients functionally in Classes 3 or 4 and those with auricular fibrillation should be advised against undertaking pregnancy. Therapeutic abortion is indicated in such patients who have not passed the fourth month. Conservative management is usually advisable beyond this time. The earliest signs of heart failure are an indication for digitalis administration. In acute pulmonary edema digitalis intravenously, oxygen by positive pressure mask, intravenous aminophylline, and mercurial diuretics may be life saving. Careful prenatal observation with the prevention and early control of acute respiratory infections is most important in reducing the incidence of heart failure.

SCHWARTZ

Aspitarte, A., Sanchez Agesta, A., and Andres Lujan, M.: Acute Benign Pericarditis. Rev. españ. de cardiol. **4**: 1 (Jan.–Feb.), 1950.

The authors present 7 cases of pericarditis, which correspond in their clinical and laboratory findings to a condition which has been described as "acute benign pericarditis," "primary or idiopathic pericarditis" or "non-specific pericarditis." Frequently an infection of the respiratory tract anteceded the onset. The pain at times simulated myocardial infarction, but usually was more diffuse, less dramatic and did not show the typical radiation of that seen in myocardial infarction. Pericardial effusion was present in most cases. Sometimes the electrocardiographic findings were of very short duration. There was a tendency to recurrence. One case, typical in every respect of this condition, resulted in complete recovery, but pulmonary tuberculosis developed a year later. As in the "idiopathic pleurisy" which is so frequently tuberculous in nature, the authors believe that in this condition a tuberculous infection may be the primary cause.

ULLMANN

Southwick, H. W.: A Clamp for the Construction of Vascular Anastomoses. Arch. Surg. **60**: 372 (Feb.), 1950.

The author describes a clamp which can be used in the isolation of a segment of two adjacent vessels and thus allow the construction of an anastomosis between them without mobilization or temporary ligation of either. It can be applied without injuring the vessel wall since it has a great number of fine teeth. It is in 2 parts so as to allow for easy application and removal.

ABRAMSON

Shapiro, A. L., and Robillard, G. L.: The Esophageal Arteries. Their Configurational Anatomy and Variations in Relation to Surgery. Ann. Surg. **131**: 171 (Feb.), 1950.

On the basis of anatomic dissections of 50 cadavers, together with radiographic study of arteries injected with barium sulfate, the authors present a description of the arterial blood supply of the esophagus. For the purpose of the study, the esophagus is divided into 4 parts: pars cervicalis, pars bifurcalis, pars thoracalis and pars abdominalis. The pars cervicalis receives its blood supply primarily from the inferior thyroid artery which arises from the thyrocervical trunk of the subclavian artery. The primary supply to the pars bifurcalis is from the bronchial arteries which are branches either of the aorta or of the right third or fourth intercostal artery. The blood supply to the pars thoracalis arises mainly from the superior and inferior esophageal arteries, while that to the pars abdominalis generally comes from the left gastric artery.

The esophageal circulation is best considered as a shared vasculature, and therefore care must be taken during surgical mobilization in separating the esophagus from such embryologically related structures as the trachea, bronchi and diaphragm. Otherwise the freed segments might be devascularized to a degree incompatible with reparative processes.

ABRAMSON

Turner, G. S., and Pentz, E. I.: Effect of Cholesterol on Antigenicity of Streptolysin O. Proc. Soc. Exper. Biol. & Med. **73**: 169 (Feb.), 1950.

The authors confirmed the previous observation that cholesterol neutralizes the hemolytic activity of streptolysin O. The antigenicity of streptolysin O is not impaired in the cholesterol-neutralized mixtures. The explanation offered is that some easily dissociated streptolysin-choesterol complex is formed

which loses its ability to lyse red cells but still functions as an antigen. In cholesterol-neutralized mixtures, streptolysin O neutralized by its specific antibody elicits virtually no immune response to streptolysin O.

MINTZ

McKee, F. W., Wilt, W. G., Jr., Hyatt, R. E., and Whipple, G. H.: The Circulation of Ascitic Fluid. Interchange of Plasma and Ascitic Fluid Protein as Studied by Means of C^{14}-Labeled Lysine in Dogs with Constriction of the Vena Cava. J. Exper. Med. **91:** 115 (Feb.), 1950.

The authors have demonstrated an ascitic fluid circulation in experiments indicating a rapid exchange of protein between the ascitic pool and circulating plasma. Plasma containing plasma proteins labeled with radioactive lysine was given either intraperitoneally or intravenously to dogs previously made ascitic by an aluminum band constricting the vena cava above the diaphragm. There was evidence that 30 to 40 per cent of the labeled protein crossed from the ascitic fluid to the plasma, or in the opposite direction, in 48 to 72 hours.

Many factors influence the production and accumulation of ascites and absorption. In human ascites inflammation is an important factor at times, and further experiments are necessary to evaluate the exact role of this factor.

SCHWARTZ

Fuhrman, F. A., and Crismon, J. M.: Electrolyte, Water and Glycogen in Rat Muscle following Ligation of Major Arteries and Veins. Proc. Soc. Exper. Biol. & Med. **73:** 462 (March), 1950.

Ligation of the femoral artery, the common iliac artery and vein or the femoral, popliteal and saphenous arteries and veins in albino rats resulted in only slight alteration in the sodium, potassium and water content of the gastrocnemius and anterior tibial muscles four days after occlusion. Muscle glycogen was reduced in one-half the animals when the femoral artery was ligated. Ligation of the femoral, popliteal and saphenous arteries and veins caused edema in only 1 animal and the extra sodium found in the muscle was accounted for by the increase in extracellular fluid. Since neither gangrene nor permanent functional impairment occurred, it is apparent that collateral circulation in the albino rat is sufficient to maintain the integrity of the leg muscles after loss of their major blood supply.

MINTZ

Borden, C. W., Ebert, R. V., Welsen, R. H., and Wells, H. S.: Pulmonary Hypertension in Heart Disease. New England J. Med. **242:** 529 (April), 1950.

The purpose of this study was to correlate pulmonary artery pressure with the physical status as well as clinical manifestations in patients with mitral valve disease. Pulmonary artery pressures were obtained by the catherization technic. The criteria of the New York Heart Association was utilized as a measure of the functional capacity of the heart. In a group of 31 patients a rough linear correlation was found to be present between the pulmonary artery pressure and the functional capacity of the heart. The cardiac output was determined in 15 of these patients. Of those in groups I and II (functional capacity) the cardiac index averaged 3.2 liters per minute, whereas those in groups III and IV showed only 2.3 liters per minute. When the pulmonary artery pressure was correlated with the vital capacity, the relation was not striking since certain patients with marked increased vital capacities showed only slightly elevated or normal pulmonary artery pressures. Five patients with frank hemoptysis all showed marked pulmonary hypertension. In a group showing left ventricular failure the pulmonary artery pressure was not as elevated as in the mitral stenosis group. Evidence is presented suggesting that elevation of the pulmonary artery pressure in mitral stenosis is due to increase in peripheral resistance as well as increased pressure in the left auricle.

NADLER

Remington, J. W., Hamilton, W. F., Caddell, H. M., Boyd, G. H., Jr., Wheeler, N. C., and Pickering, R. W.: Vasoconstriction as a Precipitating Factor in Traumatic Shock in the Dog. Am. J. Physiol. **161:** 125 (April), 1950.

Traumatic shock due to (a) visceral trauma by digital manipulation of the celiac axis, adrenal region, and gall bladder and (b) multiple mild blows to the legs of the animals was induced in a total of 16 anaesthetized dogs. Following trauma, a sharp increase in peripheral resistance and a fall in peripheral flow were uniformly noted, the values exceeding those obtained in hemorrhagic shock. The magnitude of resistance changes suggested rather wide spread vasoconstriction. Small doses of Dibenamine (5 mg. per Kg.) prevented the initial rise of peripheral resistance and contributed substantially to the survival of the animals (0 in controls, 89 per cent in dogs receiving Dibenamine).

HECHT

Woolsey, T. D.: Statistical Studies of Heart Disease VI. Age at Onset of Heart and Other Cardiovascular-Renal Diseases. Pub. Health Rep. **65:** 555 (April), 1950.

During 1935–1936 the National Health Survey visited 700,000 households throughout the country. This report is one of a series of analyses of data accumulated thereby.

Prevalence rates by age were multiplied by numbers of persons surviving to each age, as determined from life tables. These figures, with estimates of deaths among heart disease patients at each age, were used to compute approximate probabilities of

acquiring the disease at each age group. It was found that a 25 year old male has a 60 per cent chance of subsequently acquiring heart disease; the chance is 61.8 per cent for a female. At age 50 the chances are 63.8 per cent and 65.5 per cent, respectively. Hypertension may be expected in 47.8 per cent of males and 54.7 per cent of females at age 25. At that age the chances for developing nephritis are 22.7 per cent for males and 25.2 per cent for females. Since the data was accumulated by household surveys it is likely that they are minimal figures.

WAIFE

Remington, J. W., Hamilton, W. F., Caddell, H. M., Boyd, G. H., Jr., and Hamilton, W. F., Jr.: Some Circulatory Responses to Hemorrhage in the Dog. Am. J. Physiol. **161:** 106 (April), 1950.

Thirty seven anesthetized dogs were subjected to repeated hemorrhages until death. (5 cc. per Kg. at 10 minute intervals until arterial pressures fell below 50 mm. Hg.). Optical pressure records were obtained and cardiac output determined by direct Fick methods (dye and catheter) or by analysis of pressure pulses. Total peripheral resistance was calculated in the usual manner.

Three shock phases were recognized: phase I showed little decline in pressure, slight fall in cardiac output and an increase in peripheral resistance of approximately 10 per cent. Phase II showed cardioacceleration with fall in mean arterial pressures and usually a slight increase in cardiac output. Peripheral resistance varied, demonstrating a reciprocal relation between resistance and flow, with high resistance in examples of low output and low resistance with high output. While dye dilution technics and heart volume measurements by x-ray demonstrated a decrease in large vessel-lung-heart volume in the first phase, it was estimated that during the second phase heart blood accounted for 23 per cent of the hemorrhage. In the terminal phase III, a sharp decline in cardiac output and in peripheral resistance was uniformly evident. During this phase oxygen consumption, and mixed venous oxygen content, particularly, fell to extremely low levels. Total oxygen transport (cardiac output times arterial oxygen content), originally about 3.5 times the oxygen consumption, fell to less than the initial consumption at the end of phase III.

The authors conclude that the experiments failed to demonstrate striking arteriolar constriction as one of the constant findings of early hemorrhagic shock. Late failure of arteriolar tone precipitates the final circulatory crisis.

HECHT

Marquardt, P., and Wachtel, H. J.: A Method of Registration of the Heart Rate. Arch. internat. de. pharmacodyn. et de. thérap. **82:** 80 (April), 1950.

The authors devised a method for simultaneous registration of heart rate and stroke volume in the isolated frog's heart. While one end of a lever connected with the preparation registers the magnitude of the contraction, the opposite end of the lever writes a time signal by dipping a platinum wire into a mercury container, thus closing an electric circuit. It could be demonstrated by this method that in the frog's heart, following strophanthin K, a decrease of heart rate precedes the increment of stroke volume.

PICK

Draper, A. J.: The Cardioinhibitory Carotid Sinus Syndrome. Ann. Int. Med. **32:** 700 (April), 1950.

The author summarizes the clinical features and electrocardiographic findings in 11 cases of the cardioinhibitory carotid sinus syndrome. The diagnosis was based upon the occurrence of spontaneous syncopal attacks, the reproduction of the syncopal attacks by pressure over one or the other carotid sinus, and the electrocardiographic registration of cardiac standstill during mechanical stimulation of the carotid sinus. The spontaneous or induced cardiac standstill in these cases is attributed to a state of increased sensitivity of vagal nerve endings in the heart, which results is exaggerated cardioinhibitory effects in response to various stimuli. In most of the patients in this group, there were findings to indicate that they were also suffering from myocardial and/or coronary artery disease. Organic heart disease should, therefore, be suspected in all patients exhibiting the cardioinhibitory carotid sinus syndrome and, conversely, the syndrome should be sought whenever a diagnosis of hypertensive or arteriosclerotic heart disease is made.

WENDKOS

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COMMITTEE ON CARDIOVASCULAR CLINICS

The Executive Committee of the Committee on Cardiovascular Clinics of the Association's Scientific Council will hold its first meeting in January or February, 1951. At this meeting applications for approval of clinics which have been submitted by affiliated heart associations prior to January 1 will be considered.

Dr. H. M. Marvin, Chairman of the Scientific Council, has appointed the following persons to serve as members of the Executive Committee: Floyd C. Beelman, M.D., Topeka; Edward F. Bland, M.D., Boston; Herbert Chasis, M.D., New York; Mrs. Myrtle H. Coe. Minneapolis; Richard D. Friedlander, M.D., San Francisco; Miss Muriel Gayford, Bryn Mawr, Pa.; Chester M. Kurtz, M.D., Madison. Wis.; Hugh Montgomery, M.D., Philadelphia.

Information regarding procedures for clinic approval may be obtained from affiliated heart associations.

LOUISIANA FELLOWSHIP

The Louisiana Heart Association announces two fellowships in cardiology, to be known as the Charles Payne Fenner Jr. Memorial Fellowship and the Leon H. Rittenberg Fellowship. Each is in the amount of $2,400.00 to $3,000.00 for a one-year duration. They are open to doctors having previously served at least one year of internship and one or more years of formal resident training in internal medicine or pediatrics. The purpose is to further research and provide additional clinical training in cardiovascular disease. Applications should be mailed to Dr. Allan M. Goldman, Secretary-Treasurer, Louisiana Heart Association, 3439 Prytania Street, New Orleans, La.